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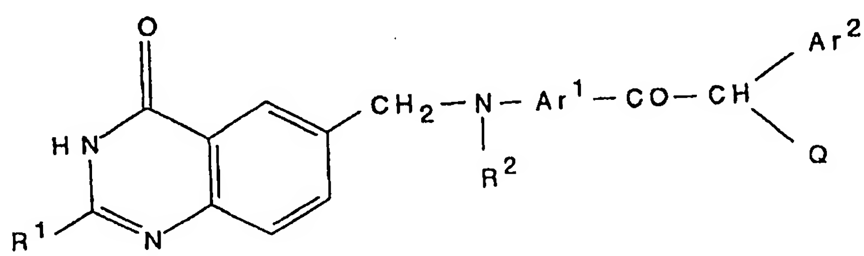
(54) **Quinazoline derivatives**

(57) Quinazoline derivatives of the formula I



wherein
R^1 is hydrogen or a defined substituent, e.g. amino, (1 - 4C) alkyl and (1 - 4C) alkoxy;
R^2 is hydrogen, (1 - 4C) alkyl, which can be substituted by certain substituents (3 - 4C) alkenyl or (3 - 4C) alkynyl;
Ar^1 is phenylene or a 5- or 6-membered aromatic heterocyclene ring;
Ar^2 is optionally substituted phenyl or heteroaryl; and
Q is a defined substituent e.g. nitro, cyano, carbamoyl, (1 - 4C) alkylsulphonyl and N,N-di-[(1 - 4C) alkyl]sulphamoyl;
or pharmaceutically-acceptable salts thereof; are useful as anti-tumour agents.

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QUINAZOLINE DERIVATIVES

This invention relates to quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-tumour activity. The invention includes quinazoline derivatives and processes for their manufacture, pharmaceutical compositions containing said quinazoline derivatives and the use of said quinazoline derivatives in the manufacture of medicaments for use in the production of an anti-tumour effect in a warm-blooded animal such as man.

One group of anti-tumour compounds comprises the antimetabolites, such as aminopterin and methotrexate, which are inhibitors of enzymes which utilise folic acid derivatives. A newer compound of this type which showed considerable promise in clinical trials is known as CB3717 and is described and claimed in United Kingdom Patent Specification No. 2065653B. Despite its promising activity against human breast, ovarian and liver cancer however, CB3717 shows symptoms of toxicity in humans, particularly in relation to the liver and kidney [Calvert, Alison, Harland, Robinson, Jackman, Jones, Newell, Siddik, Whiltshaw, McElwain, Smith and Harrap, J. Clin. Oncol., 1986, 4, 1245; Cantwell, Earnshaw and Harris, Cancer Treatment Reports, 1986, 70, 1335; Bassendine, Curtin, Loose, Harris and James, J. Hepatol., 1987, 4, 39; Vest, Bork and Hasen, Eur. J. Cancer Clin. Oncol., 1988, 24, 201; Cantwell, Macaulay, Harris, Kaye, Smith, Milsted and Calvert, Eur. J. Cancer Clin. Oncol., 1988, 24, 733; Sessa, Zucchetti, Ginier, Willems, D'Incalci and Cavalli, Eur. J. Cancer Clin. Oncol., 1988, 24, 769]. Such adverse side effects are reduced in compounds in which the 2-amino substituent of CB3717 is either missing or is replaced by one of various alternative substituents as disclosed respectively in United Kingdom Patent Specification Nos. 2175903 and 2188319.

Compounds of the CB3717-type are believed to act as anti-tumour agents by inhibiting the enzyme thymidylate synthase, which enzyme catalyses the methylation of deoxyuridine monophosphate to produce thymidine monophosphate which is required for DNA synthesis. The anti-tumour activity of CB3717 may be assessed *in*

vitro by determining its inhibitory effect on that enzyme, and in cell cultures by its inhibitory effect on cancer cell lines such as the mouse leukaemia cell line L1210, the mouse lymphoma cell lines L5178Y TK-/- and L5178Y TK +/- and the human breast cancer cell line MCF-7.

Other compounds of the CB3717-type may therefore have their anti-tumour activity assessed and compared with that of CB3717 by their activity against, for example, the same enzyme and the same cancer cell lines.

Antimetabolites, such as aminopterin and methotrexate, which are inhibitors of enzymes which utilise folic acid derivatives, have also shown promise in the treatment of various allergic diseases such as allergic rhinitis, atopic dermatitis and psoriasis. The quinazoline derivatives of the present invention, being antimetabolites, are thus of value as therapeutic agents in the treatment of, for example, allergic conditions such as psoriasis.

Antimetabolites such as methotrexate have also shown promise in the treatment of various inflammatory diseases such as inflammation of the joints (especially rheumatoid arthritis, osteoarthritis and gout) and inflammation of the gastrointestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis) [Weinblatt et al., New England J. Med., 1985, 312, 818; Andersen et al., Ann. Internat. Med., 1985, 103, 489; Healey, Bull Rheum. Dis., 1986, 36, 1]. The quinazoline derivatives of the present invention are thus of value as therapeutic agents in the treatment of, for example, inflammatory conditions such as rheumatoid arthritis.

European Patent Application No. 0316657 (published 24 May 89) discloses a series of quinazoline derivatives which lack the amino acid residue of compounds of the CB3717-type. The disclosed compounds are reported to possess inhibitory activity against thymidylate synthase. Among the disclosed compounds are quinazoline derivatives wherein the amino acid residue of compounds of the CB3717-type is replaced by a residue derived from 5-aminotetrazole.

It is also known from European Patent Application No. 0365763 (published 02 May 90) that quinazoline derivatives of, for example, the CB3717-type, but wherein the amino acid residue, has been replaced by, for example, a halogeno, cyano or phenylsulphonyl

residue, retain activity against thymidylate synthase and the L1210 cell-line.

We have now found that the quinazoline derivatives of the present invention possess CB3717-type activity.

According to the invention there is provided a quinazoline derivative of the formula I (set out hereinafter)
wherein R^1 is hydrogen, amino, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, piperidino, morpholino, piperazin-1-yl, 4-[(1-4C)alkyl]piperazin-1-yl, 4-[(2-4C)alkanoyl]piperazin-1-yl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, piperidino-(1-4C)alkyl, morpholino-(1-4C)alkyl, piperazin-1-yl-(1-4C)alkyl, 4-[(1-4C)alkyl]piperazin-1-yl-(1-4C)alkyl, 4-[(2-4C)alkanoyl]piperazin-1-yl-(1-4C)alkyl, _N_-[hydroxy-(2-4C)alkyl]amino-(1-4C)alkyl, _N_-[hydroxy-(2-4C)alkyl]-_N_-(1-4C)alkylamino-(1-4C)alkyl, _N_,_N_-di-[hydroxy-(2-4C)alkyl]amino-(1-4C)alkyl, _N_-[(1-4C)alkoxy-(2-4C)alkyl]amino-(1-4C)alkyl, _N_-[(1-4C)alkoxy-(2-4C)alkyl]-_N_-(1-4C)alkylamino-(1-4C)alkyl, _N_,_N_-di-[(1-4C)alkoxy-(2-4C)alkyl]amino-(1-4C)alkyl, _N_-[(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl, _N_-[(1-4C)alkylamino-(2-4C)alkyl]-_N_-(1-4C)alkylamino-(1-4C)alkyl, _N_,_N_-di-[(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl, _N_-[di-(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl, _N_-[di-(1-4C)alkylamino-(2-4C)alkyl]-_N_-(1-4C)alkylamino-(1-4C)alkyl, _N_,_N_-di-[di-(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)alkyl, carboxy-(2-4C)alkanoyloxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(2-4C)alkanoyloxy-(1-4C)alkyl, hydroxy-(2-4C)alkoxy-(1-4C)alkyl or (1-4C)alkoxy-(2-4C)alkoxy-(1-4C)alkyl;
the quinazoline ring may optionally bear at the 5-, 7- or 8-position one further substituent selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy;
R^2 is hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-4C)alkynyl, hydroxy-(2-4C)alkyl, halogeno-(2-4C)alkyl or cyano-(1-4C)alkyl;
Ar^1 is phenylene or a 5- or 6-membered aromatic heterocyclene ring

which contains up to 3 heteroatoms selected from nitrogen and sulphur, each of which may optionally bear one or two substituents selected from halogeno, hydroxy, amino, nitro, cyano, trifluoromethyl, (1-4C)alkyl and (1-4C)alkoxy;

Ar^2 is phenyl or heteroaryl which may optionally bear one or two substituents selected from halogeno, hydroxy, amino, nitro, cyano, trifluoromethyl, (1-4C)alkyl and (1-4C)alkoxy; and

Q is nitro, cyano, carbamoyl, sulphamoyl, (1-4C)alkoxycarbonyl, di-[(1-4C)alkoxy]phosphoryl, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, phenyl-(1-4C)alkylthio, phenyl-(1-4C)alkylsulphinyl, phenyl-(1-4C)-alkylsulphonyl, heteroarylthio, heteroarylsulphinyl, heteroarylsulphonyl, heteroaryl-(1-4C)alkylthio, heteroaryl-(1-4C)alkylsulphinyl, heteroaryl-(1-4C)alkylsulphonyl, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, N-(1-4C)alkylsulphamoyl, N,N-di-[(1-4C)alkyl]sulphamoyl, morpholino-sulphonyl, piperidinosulphonyl, piperazin-1-ylsulphonyl or 4-(1-4C)-alkylpiperazin-1-ylsulphonyl, and when Q is a group comprising a phenyl or heteroaryl group, said phenyl or heteroaryl group may optionally bear one substituent selected from halogeno, cyano, hydroxy, amino, (1-4C)alkyl and (1-4C)alkoxy;

and wherein the heteroaryl group when Ar^2 is heteroaryl, or the heteroaryl group when Q is a heteroaryl-containing group, is a 5- or 6-membered heteroaryl ring which contains 1 or 2 nitrogen heteroatoms and optionally contains a further heteroatom selected from nitrogen, oxygen and sulphur;

or a pharmaceutically-acceptable salt thereof.

In a further embodiment of the invention there is provided a quinazoline derivative of the formula I as defined hereinbefore wherein, in addition, Q is 4-(1-4C)alkoxycarbonylpiperazin-1-ylsulphonyl, N-[amino-(2-4C)alkyl]sulphamoyl, N-[(1-4C)alkylamino-(2-4C)alkyl]sulphamoyl, N-{di-[(1-4C)alkyl]amino-(2-4C)alkyl}sulphamoyl, N-(1-4C)alkyl-N-[amino-(2-4C)alkyl]sulphamoyl, N-(1-4C)alkyl-N-[(1-4C)alkylamino-(2-4C)alkyl]sulphamoyl or N-(1-4C)alkyl-N-{di-[(1-4C)alkyl]amino-(2-4C)alkyl}sulphamoyl;

or a pharmaceutically-acceptable salt thereof.

The chemical formulae referred to herein by Roman numerals are set out for convenience on a separate sheet hereinafter. In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms.

It will be observed that a quinazoline derivative of the invention may possess one or more asymmetric carbon atoms and it can therefore exist in racemic and optically active forms. It is to be understood that this invention encompasses a racemic form of the quinazoline derivative and any optically-active form thereof which possesses anti-tumour activity, it being a matter of common general knowledge how a racemic compound may be separated into its optically-active forms.

It will also be observed that a quinazoline derivative of the invention by virtue of the -CO-CH< group may exist in an enolic form or in an equilibrium mixture of the enolic and ketonic forms. It is to be understood that this invention encompasses a compound of the invention, whether it is in an enolic form, a ketonic form or a mixture thereof, which possesses anti-tumour activity.

Within the present invention it is to be understood that a quinazoline derivative of the formula I may exhibit the phenomenon of tautomerism and that the formulae drawings presented within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which possesses anti-tumour activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings.

It is also to be understood that certain quinazoline derivatives of the formula I can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess anti-tumour activity.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for R^1 or R^2 when it is (1-4C)alkyl, or for

a (1-4C)alkyl substituent which may be present on the quinazoline ring, on Ar^1 or Ar^2 or on a phenyl-containing or heteroaryl-containing group in Q, is, for example, methyl, ethyl, propyl, isopropyl or butyl.

A suitable value for R^1 when it is (1-4C)alkoxy, or for a (1-4C)alkoxy substituent which may be present on the quinazoline ring, on Ar^1 or Ar^2 or on a phenyl-containing or heteroaryl-containing group in Q, is, for example, methoxy, ethoxy, propoxy, isopropoxy or butoxy.

A suitable value for a halogeno substituent which may be present on the quinazoline ring, on Ar^1 or Ar^2 or on a phenyl-containing or heteroaryl-containing group in Q, is, for example, fluoro, chloro or bromo.

A suitable value for R^1 when it is (1-4C)alkylamino is, for example, methylamino, ethylamino, propylamino or isopropylamino; when it is di-[(1-4C)alkyl]amino is, for example, dimethylamino, N-ethyl-N-methylamino or diethylamino; when it is 4-[(1-4C)alkyl]piperazin-1-yl is, for example, 4-methylpiperazin-1-yl or 4-ethylpiperazin-1-yl; and when it is 4-[(2-4C)alkanoyl]-piperazin-1-yl is, for example, 4-acetylpiperazin-1-yl or 4-propionylpiperazin-1-yl.

A suitable value for R^1 when it is hydroxy-(1-4C)alkyl is, for example, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl or 3-hydroxypropyl; when it is (1-4C)alkoxy-(1-4C)alkyl is, for example, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl or 3-methoxypropyl; when it is amino-(1-4C)alkyl is, for example, aminomethyl, 1-aminoethyl, 2-aminoethyl or 3-aminopropyl; when it is (1-4C)alkylamino-(1-4C)alkyl is, for example, methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl or 3-methylaminopropyl; and when it is di-[(1-4C)alkyl]amino-(1-4C)alkyl is, for example, dimethylaminomethyl, N-ethyl-N-methylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl, 2-diethylaminoethyl or 3-dimethylaminopropyl.

A suitable value for R^1 when it is piperidino-(1-4C)alkyl is, for example, piperidinomethyl, 1-piperidinoethyl, 2-piperidinoethyl or 3-piperidinopropyl;

when it is morpholino-(1-4C)alkyl is, for example, morpholinomethyl, 1-morpholinoethyl, 2-morpholinoethyl or 3-morpholinopropyl; when it is piperazin-1-yl-(1-4C)alkyl is, for example, piperazin-1-ylmethyl, 1-(piperazin-1-yl)ethyl, 2-(piperazin-1-yl)ethyl or 3-(piperazin-1-yl)propyl; when it is 4-[(1-4C)alkyl]piperazin-1-yl-(1-4C)alkyl is, for example, 4-methylpiperazin-1-ylmethyl, 4-ethylpiperazin-1-ylmethyl, 1-(4-methylpiperazin-1-yl)ethyl, 2-(4-methylpiperazin-1-yl)ethyl or 2-(4-ethylpiperazin-1-yl)ethyl; and when it is 4-[(2-4C)alkanoyl]piperazin-1-yl-(1-4C)alkyl is, for example, 4-acetylpiperazin-1-ylmethyl, 1-(4-acetylpiperazin-1-yl)-ethyl, 2-(4-acetylpiperazin-1-yl)ethyl or 2-(4-propionylpiperazin-1-yl)ethyl.

A suitable value for R^1 when it is N-[hydroxy-(2-4C)-alkyl]amino-(1-4C)alkyl is, for example, N-(2-hydroxyethyl)-aminomethyl, N-(3-hydroxypropyl)aminomethyl, 1-[N-(2-hydroxy-ethyl)amino]ethyl, 2-[N-(2-hydroxyethyl)amino]ethyl or 3-[N-(2-hydroxyethyl)amino]propyl; when it is N-[hydroxy-(2-4C)-alkyl]-N-(1-4C)alkylamino-(1-4C)alkyl is, for example, N-(2-hydroxyethyl)-N-methylaminomethyl, N-(3-hydroxypropyl)-N-methylaminomethyl, N-(2-hydroxyethyl)-N-ethylaminomethyl, 1-[N-(2-hydroxyethyl-N-methylamino]ethyl, 2-[N-(2-hydroxyethyl)-N-methylamino]ethyl, 2-[N-(3-hydroxypropyl)-N-methylamino]ethyl or 3-[N-(2-hydroxyethyl)-N-methylamino]propyl; and when it is N,N-di-[hydroxy-(2-4C)alkyl]amino-(1-4C)alkyl is, for example, N,N-di-(2-hydroxyethyl)aminomethyl, N,N-di-(3-hydroxypropyl)-aminomethyl, 1-[N,N-di-(2-hydroxyethyl)amino]ethyl, 2-[N,N-di-(2-hydroxyethyl)amino]ethyl, 2-[N,N-di(3-hydroxypropyl)-amino]ethyl or 3-[N,N-di-(2-hydroxyethyl)amino]propyl.

A suitable value for R^1 when it is N-[(1-4C)alkoxy-(2-4C)alkyl]amino-(1-4C)alkyl is, for example, N-(2-methoxyethyl)aminomethyl, N-(2-ethoxyethyl)aminomethyl, N-(3-methoxypropyl)aminomethyl, 1-[N-(2-methoxyethyl)amino]ethyl, 2-[N-(2-methoxyethyl)amino]ethyl, 2-[N-(2-ethoxyethyl)amino]ethyl, 2-[N-(3-methoxypropyl)amino]ethyl or 3-[N-(2-methoxyethyl)amino]-propyl; when it is N-[(1-4C)alkoxy-(2-4C)alkyl]-N-(1-4C)alkyl-amino-(1-4C)alkyl is, for example, N-(2-methoxyethyl)-N-methyl-

aminomethyl, N-(3-methoxypropyl)-N-methylaminomethyl, N-(2-methoxyethyl)-N-ethylaminomethyl, 2-[N-(2-methoxyethyl)-N-methylamino]ethyl or 3-[N-(2-methoxyethyl)-N-methylamino]propyl; and when it is N,N-di-[(1-4C)alkoxy-(2-4C)alkyl]amino-(1-4C)alkyl is, for example, N,N-di-(2-methoxyethyl)aminomethyl, N,N-di-(2-ethoxyethyl)aminomethyl, N,N-di-(3-methoxypropyl)aminomethyl, 2-[N,N-di-(2-methoxyethyl)amino]ethyl, 2-[N,N-di-(2-ethoxyethyl)amino]ethyl, 2-[N,N-di-(3-methoxypropyl)amino]ethyl or 3-[N,N-di-(2-methoxyethyl)amino]propyl.

A suitable value for R^1 when it is N-[(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl is, for example, N-(2-methylaminoethyl)aminomethyl, N-(2-ethylaminoethyl)aminomethyl, N-(3-methylaminopropyl)aminomethyl, 1-[N-(2-methylaminoethyl)-amino]ethyl, 2-[N-(2-methylaminoethyl)amino]ethyl, 2-[N-(2-ethylaminoethyl)amino]ethyl, 2-[N-(3-methylaminopropyl)amino]ethyl or 3-[N-(2-methylaminoethyl)amino]propyl; when it is N-[(1-4C)alkylamino-(2-4C)alkyl]-N-(1-4C)alkylamino-(1-4C)alkyl is, for example, N-(2-methylaminoethyl)-N-methylaminomethyl, N-(3-methylaminopropyl)-N-methylaminomethyl, N-(2-methylaminoethyl)-N-ethylaminomethyl, N-(2-ethylaminoethyl)-N-methylaminomethyl, 2-[N-(2-methylaminoethyl)-N-methylamino]ethyl, 2-[N-(3-methylaminopropyl)-N-methylamino]ethyl or 3-[N-(2-methylaminoethyl)-N-methylamino]propyl; and when it is N,N-di-[(1-4C)alkylamino-(2-4C)-alkyl]amino-(1-4C)alkyl is, for example, N,N-di-(2-methylaminoethyl)aminomethyl, N,N-di-(2-ethylaminoethyl)aminomethyl, N,N-di-(3-methylaminopropyl)aminomethyl, 2-[N,N-di-(2-methylaminoethyl)amino]ethyl, 2-[N,N-di-(2-ethylaminoethyl)amino]ethyl, 2-[N,N-di-(3-methylaminopropyl)amino]ethyl or 3-[N,N-di-(2-methylaminoethyl)amino]propyl.

A suitable value for R^1 when it is N-[di-(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl is, for example, N-(2-dimethylaminoethyl)aminomethyl, N-(2-diethylaminoethyl)aminomethyl, N-(3-dimethylaminopropyl)aminomethyl, 2-[N-(2-dimethylaminoethyl)-amino]ethyl, 2-[N-(3-dimethylaminopropyl)amino]ethyl or 3-[N-(2-dimethylaminoethyl)amino]propyl; when it is N-[di-(1-4C)alkylamino-(2-4C)alkyl]-N-(1-4C)alkylamino-(1-4C)alkyl is,

for example, N-(2-dimethylaminoethyl)-N-methylaminomethyl, N-(3-dimethylaminopropyl)-N-methylaminomethyl, N-(2-dimethylamino-ethyl-N-ethylaminomethyl, N-(2-diethylaminoethyl)-N-methylaminomethyl, 2-[N-(2-dimethylaminoethyl)-N-methylamino]ethyl or 3-[N-(2-dimethylaminoethyl)-N-methylamino]propyl; and when it is N,N-di-[di-(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl is, for example, N,N-di-(2-dimethylaminoethyl)aminomethyl, N,N-di-(2-diethylaminoethyl)aminomethyl, N,N-di-(3-dimethylamino-propyl)aminomethyl, 2-[N,N-di-(2-dimethylaminoethyl)amino]ethyl, 2-[N,N-di-(3-dimethylaminopropyl)amino]ethyl or 3-[N,N-di-(2-dimethylaminoethyl)amino]propyl.

A suitable value for R^1 when it is (2-4C)alkanoyloxy-(1-4C)alkyl is, for example, acetoxymethyl, propionyloxymethyl, 1-acetoxyethyl or 2-acetoxyethyl; when it is carboxy-(2-4C)alkanoyloxy-(1-4C)alkyl is, for example, 2-carboxyacetoxymethyl, 3-carboxypropionyloxymethyl, 2-(2-carboxyacetoxy)ethyl or 2-(3-carboxypropionyloxy)ethyl; and when it is (1-4C)alkoxycarbonyl-(2-4C)alkanoyloxy-(1-4C)alkyl is, for example, 2-methoxycarbonylacetoxymethyl, 2-ethoxycarbonylacetoxy-methyl, 3-methoxycarbonylpropionyloxymethyl, 2-(2-methoxycarbonyl-acetoxy)ethyl or 2-(3-methoxycarbonylpropionyloxy)ethyl.

A suitable value for R^1 when it is hydroxy-(2-4C)-alkoxy-(1-4C)alkyl is, for example, 2-hydroxyethoxymethyl, 3-hydroxypropoxymethyl or 2-(2-hydroxyethoxy)ethyl; and when it is (1-4C)alkoxy-(2-4C)alkoxy-(1-4C)alkyl is, for example, 2-methoxyethoxymethyl, 2-ethoxyethoxymethyl, 3-methoxypropoxymethyl, 3-ethoxypropoxymethyl or 2-(2-methoxyethoxy)ethyl.

A suitable value for R^2 when it is (3-4C)alkenyl is, for example, prop-2-enyl, but-2-enyl, but-3-enyl or 2-methylprop-2-enyl; when it is (3-4C)alkynyl is, for example, prop-2-ynyl or but-3-ynyl; when it is hydroxy-(2-4C)alkyl is, for example, 2-hydroxyethyl or 3-hydroxypropyl; when it is halogeno-(2-4C)alkyl is, for example, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 3-fluoropropyl, 3-chloropropyl or 3-bromopropyl; and when it is cyano-(1-4C)alkyl is, for example, cyanomethyl, 2-cyanoethyl or 3-cyanopropyl.

A suitable value for Ar^1 when it is phenylene is, for

example 1,3- or 1,4-phenylene.

A suitable value for Ar^1 when it is a 5- or 6-membered aromatic (that is, fully unsaturated) heterocyclene ring which contains up to 3 heteroatoms selected from nitrogen and sulphur is, for example, thiophenediyl, pyridinediyl, pyrimidinediyl or thiazolediyl.

A suitable value for Ar^2 when it is heteroaryl, or for the heteroaryl group when Q is a heteroaryl-containing group, is a 5- or 6-membered heteroaryl ring which contains 1 or 2 nitrogen heteroatoms and optionally contains a further heteroatom selected from nitrogen, oxygen and sulphur, for example, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl or thiadiazolyl. The heteroaryl group may be attached through any available position including through any available nitrogen atom and the heteroaryl group may bear a substituent on any available nitrogen atom.

A suitable value for Q when it is (1-4C)alkoxycarbonyl is, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl or tert-butoxycarbonyl; when it is di-[(1-4C)alkoxy]phosphoryl is, for example, dimethoxyphosphoryl, diethoxyphosphoryl, dipropoxyphosphoryl or dibutoxyphosphoryl; when it is (1-4C)alkylthio is, for example, methylthio, ethylthio, propylthio, isopropylthio or butylthio; when it is (1-4C)alkylsulphinyl is, for example, methylsulphinyl, ethylsulphinyl, propylsulphinyl, isopropylsulphinyl or butylsulphinyl; when it is (1-4C)alkylsulphonyl is, for example, methylsulphonyl, ethylsulphonyl, propylsulphonyl, isopropylsulphonyl or butylsulphonyl; when it is phenyl-(1-4C)alkylthio is, for example, benzylthio, phenethylthio or 3-phenylpropylthio; when it is phenyl-(1-4C)alkylsulphinyl is, for example, benzylsulphinyl, phenethylsulphinyl or 3-phenylpropylsulphinyl; when it is phenyl-(1-4C)alkylsulphonyl is, for example, benzylsulphonyl, phenethylsulphonyl or 3-phenylpropylsulphonyl; when it is N-(1-4C)alkylcarbamoyl is, for example, N-methylcarbamoyl, N-ethylcarbamoyl or N-propylcarbamoyl; when it is N,N-di-[(1-4C)alkyl]carbamoyl is, for example, N,N-dimethylcarbamoyl,

N,N-diethylcarbamoyl or N,N-dipropylcarbamoyl; when it is N-(1-4C)-alkylsulphamoyl is, for example, N-methylsulphamoyl, N-ethylsulphamoyl or N-propylsulphamoyl; when it is N,N-di[(1-4C)alkyl]sulphamoyl is, for example, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl or N,N-dipropylsulphamoyl; and when it is 4-(1-4C)alkylpiperazin-1-yl-sulphonyl is, for example, 4-methyl-, 4-ethyl- or 4-propylpiperazin-1-ylsulphonyl.

A suitable value for Q when it is a heteroaryl-(1-4C)alkylthio group is, for example, heteroarylmethylthio or 2-heteroarylethylthio; when it is a heteroaryl-(1-4C)alkylsulphinyl group is, for example, heteroarylmethylsulphinyl or 2-heteroaryl-ethylsulphinyl; and when it is a heteroaryl-(1-4C)alkylsulphonyl group is, for example, heteroarylmethylsulphonyl or 2-heteroarylethylsulphonyl.

A suitable value for Q when it is 4-(1-4C)alkoxycarbonyl-piperazin-1-ylsulphonyl is, for example, 4-methoxycarbonyl-, 4-ethoxycarbonyl-, 4-propoxycarbonyl-, 4-butoxycarbonyl- or 4-tert-butoxycarbonyl-piperazin-1-ylsulphonyl; when it is N-[amino-(2-4C)alkyl]sulphamoyl is, for example N-(2-aminoethyl)sulphamoyl or N-(3-aminopropyl)sulphamoyl); when it is N-[(1-4C)alkylamino-(2-4C)alkyl]sulphamoyl is, for example, N-(2-methylaminoethyl)sulphamoyl, N-(2-ethylaminoethyl)sulphamoyl or N-(3-methylaminopropyl)sulphamoyl; when it is N-{di-[(1-4C)alkyl]amino-(2-4C)alkyl}sulphamoyl is, for example, N-(2-dimethylaminoethyl)sulphamoyl, N-(2-diethylaminoethyl)sulphamoyl or N-(3-dimethylaminopropyl)sulphamoyl; when it is N-(1-4C)alkyl-N-[amino-(2-4C)alkyl]sulphamoyl is, for example, N-methyl-N-(2-aminoethyl)sulphamoyl or N-ethyl-N-(2-aminoethyl)sulphamoyl; when it is N-(1-4C)alkyl-N-[(1-4C)alkylamino-(2-4C)alkyl]sulphamoyl is, for example, N-methyl-N-(2-methylaminoethyl)sulphamoyl or N-ethyl-N-(2-methylaminoethyl)sulphamoyl; and when it is N-(1-4C)alkyl-N-{di-[(1-4C)alkyl]amino-(2-4C)alkyl}sulphamoyl is, for example, N-methyl-N-(2-dimethylaminoethyl)sulphamoyl or N-ethyl-N-(2-dimethylaminoethyl)sulphamoyl.

A suitable pharmaceutically-acceptable salt of a quinazoline

derivative of the invention which is sufficiently basic is an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a quinazoline derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium or tetra(2-hydroxyethyl)ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, trimethylamine or tris-(2-hydroxyethyl)amine.

Particular compounds of the invention are, for example, quinazoline derivatives of the formula I wherein:-

(a) R^1 is hydrogen, amino, methyl, ethyl or methoxy and the quinazoline ring may optionally bear one further substituent selected from fluoro, chloro, bromo, methyl and methoxy; and R^2, Ar^1, Ar^2 and Q have any of the meanings defined hereinbefore or in this section concerning particular compounds of the invention;

(b) R^1 is hydroxymethyl, methoxymethyl, ethoxymethyl, aminomethyl, methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl, N-(2-hydroxyethyl)aminomethyl, N-(2-hydroxyethyl)-N-methylaminomethyl, N,N-di-(2-hydroxyethyl)-aminomethyl, N-(2-methoxyethyl)aminomethyl, N-(2-methoxyethyl)-N-methylaminomethyl, N,N-di-(2-methoxyethyl)aminomethyl, N-(2-methylaminoethyl)aminomethyl, N-(2-methylaminoethyl)-N-methylaminomethyl, N,N-di-(2-methylaminoethyl)aminomethyl, N-(2-dimethylaminoethyl)aminomethyl, N-(2-dimethylaminoethyl)-N-methylaminomethyl, N,N-di-(2-dimethylaminoethyl)aminomethyl, 2-hydroxyethoxymethyl or 2-methoxyethoxymethyl, and the quinazoline ring may optionally bear at the 7-position one further substituent selected from fluoro, chloro and methyl; and R^2, Ar^1, Ar^2 and Q have any of the meanings defined hereinbefore or in this section concerning particular compounds of the invention;

(c) R^2 is hydrogen, methyl, ethyl, propyl, prop-2-enyl, prop-2-

ynyl, 2-hydroxyethyl, 2-fluoroethyl, 2-bromoethyl or cyanomethyl; and R^1, the quinazoline ring substituents, Ar^1, Ar^2 and Q have any of the meanings defined hereinbefore or in this section concerning particular compounds of the invention;

(d) Ar^1 is 1,4-phenylene which may optionally bear one or two substituents selected from fluoro, chloro, bromo, hydroxy, amino, nitro, cyano, trifluoromethyl, methyl and methoxy, or Ar^1 is thiophenediyl, pyridinediyl or thiazolediyl; and R^1, the quinazoline ring substituents, R^2, Ar^2 and Q have any of the meanings defined hereinbefore or in this section concerning particular compounds of the invention;

(e) Ar^2 is phenyl which may optionally bear one or two substituents selected from fluoro, chloro, bromo, hydroxy, amino, cyano, nitro, trifluoromethyl, methyl, ethyl and methoxy, or Ar^2 is pyridyl, pyrimidinyl, pyrazolyl, oxazolyl, thiazolyl, oxadiazolyl or thiadiazolyl which may optionally bear one or two substituents selected from hydroxy, amino, nitro, cyano and methyl; and R^1, the quinazoline ring substituents, R^2, Ar^1 and Q have any of the meanings defined hereinbefore or in this section concerning particular compounds of the invention;

(f) Q is nitro, cyano, carbamoyl, sulphamoyl, methoxycarbonyl, ethoxycarbonyl, dimethoxyphosphoryl, diethoxyphosphoryl, methylthio, ethylthio, propylthio, isopropylthio, butylthio, methylsulphinyl, ethylsulphinyl, propylsulphinyl, isopropylsulphinyl, butylsulphinyl, methylsulphonyl, ethylsulphonyl, propylsulphonyl, isopropylsulphonyl, butylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, benzylthio, benzylsulphinyl, benzylsulphonyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl, morpholinosulphonyl, piperidinosulphonyl, piperazin-1-ylsulphonyl or 4-methylpiperazin-1-ylsulphonyl, and when Q is a group comprising a phenyl group (such as phenyl or benzyl), said phenyl group may optionally bear one substituent selected from fluoro, chloro, cyano, methyl and methoxy; and R^1, the quinazoline ring subsituents, R^2, Ar^1 and Ar^2 have any of the meanings defined hereinbefore or in this section concerning particular compounds of the invention; or

(g) Q is nitro, cyano, carbamoyl, sulphamoyl, methoxycarbonyl, ethoxycarbonyl, dimethoxyphosphoryl, diethoxyphosphoryl, methylthio, ethylthio, propylthio, isopropylthio, butylthio, methylsulphinyl, ethylsulphinyl, propylsulphinyl, isopropylsulphinyl, butylsulphinyl, methylsulphonyl, ethylsulphonyl, propylsulphonyl, isopropylsulphonyl, butylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, benzylthio, benzylsulphinyl, benzylsulphonyl, pyridylthio, pyridylsulphinyl, pyridylsulphonyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl, morpholinosulphonyl, piperidinosulphonyl, piperazin-1-ylsulphonyl, 4-methylpiperazin-1-ylsulphonyl, 4-tert-butoxycarbonylpiperazin-1-ylsulphonyl, N-(2-methylaminoethyl)-sulphamoyl, N-(2-dimethylaminoethyl)sulphamoyl, N-methyl-N-(2-methylaminoethyl)sulphamoyl or N-methyl-N-(2-dimethylaminoethyl)sulphamoyl, and when Q is a group comprising a phenyl group (such as phenyl or benzyl), said phenyl group may optionally bear one substituent selected from fluoro, chloro, cyano, methyl and methoxy; and R^1, the quinazoline ring subsituents, R^2, Ar^1 and Ar^2 have any of the meanings defined hereinbefore or in this section concerning particular compounds of the invention;

or a pharmaceutically-acceptable salt thereof.

A particular compound of the invention comprises a quinazoline derivative of the formula I

wherein R^1 is methyl, hydroxymethyl, methoxymethyl, methylaminomethyl, dimethylaminomethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl or 4-methylpiperazin-1-ylmethyl;

the quinazoline ring may optionally bear a 7-fluoro, 7-chloro or 7-methyl substituent;

R^2 is methyl, ethyl, propyl, prop-2-enyl or prop-2-ynyl;

Ar^1 is 1,4-phenylene which may optionally bear one fluoro substituent, or Ar^1 is thiophene-2,5-diyl or thiazole-2,5-diyl with the group -CO-CH(Ar^2)(Q) in the 2-position;

Ar^2 is phenyl which may optionally bear a substituent selected from fluoro, chloro, nitro, trifluoromethyl or methyl; and

Q is nitro, cyano, carbamoyl, sulphamoyl, methoxycarbonyl, ethoxycarbonyl, dimethoxyphosphoryl, diethoxyphosphoryl, methylsulphinyl, isopropylsulphinyl, methylsulphonyl, isopropylsulphonyl, phenylsulphinyl, phenylsulphonyl, benzylsulphinyl, benzylsulphonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, N-methylsulphamoyl, N,N-dimethylsulphamoyl or morpholinosulphonyl;
or a pharmaceutically-acceptable salt thereof.

A preferred compound of the invention comprises a quinazoline derivative of the formula I
wherein R^1 is methyl;
the quinazoline ring may optionally bear a 7-methyl substituent;
R^2 is methyl or prop-2-ynyl;
Ar^1 is 1,4-phenylene or 2-fluoro-1,4-phenylene with the group -CO-CH(Ar^2)(Q) in the 1-position;
Ar^2 is phenyl which may optionally bear a 3-nitro substituent; and
Q is diethoxyphosphoryl, isopropylsulphinyl, methylsulphonyl, isopropylsulphonyl, phenylsulphonyl, benzylsulphonyl, N-methylsulphamoyl, N,N-dimethylsulphamoyl or morpholinosulphonyl;
or a pharmaceutically-acceptable salt thereof.

A further preferred compound of the invention comprises a quinazoline derivative of the formula I
wherein R^1 is methyl;
the quinazoline ring may optionally bear a 7-methyl substituent;
R^2 is methyl or prop-2-ynyl;
Ar^1 is 1,4-phenylene, 2-fluoro-1,4-phenylene (with the group -CO-CH(Ar^2)(Q) in the 1-position) or pyridine-2,5-diyl (with the group -CO-CH(Ar^2)(Q) in the 2-position);
Ar^2 is phenyl, 3-fluorophenyl, 4-fluorophenyl, 3-nitrophenyl, 4-cyanophenyl, 2-pyridyl or 3-pyridyl; and
Q is diethoxyphosphoryl, isopropylsulphinyl, methylsulphonyl, isopropylsulphonyl, phenylsulphonyl, benzylsulphonyl, 4-pyridylsulphonyl, N-methylsulphamoyl, N,N-dimethylsulphamoyl, morpholinosulphonyl, piperazin-1-ylsulphonyl or N-methyl-N-(2-dimethylaminoethyl)sulphamoyl;
or a pharmaceutically-acceptable salt thereof.

A further preferred compound of the invention comprises a

quinazoline derivative of the formula I
wherein R^1 is methyl;
the quinazoline ring may optionally bear a 7-methyl substituent;
R^2 is methyl or prop-2-ynyl;
Ar^1 is 1,4-phenylene or 2-fluoro-1,4-phenylene with the group -CO-CH(Ar^2)(Q) in the 1-position;
Ar^2 is phenyl; and
Q is diethoxyphosphoryl, isopropylsulphinyl, methylsulphonyl, isopropylsulphonyl, phenylsulphonyl, N-methylsulphamoyl or N,N-dimethylsulphamoyl;
or a pharmaceutically-acceptable salt thereof.

A further preferred compound of the invention comprises a quinazoline derivative of the formula I
wherein R^1 is methyl;
the quinazoline ring may optionally bear a 7-methyl substituent;
R^2 is methyl or prop-2-ynyl;
Ar^1 is 1,4-phenylene, 2-fluoro-1,4-phenylene (with the group -CO-CH(Ar^2)(Q) in the 1-position) or pyridine-2,5-diyl (with the group -CO-CH(Ar^2)(Q) in the 2-position);
Ar^2 is phenyl, 3-fluorophenyl, 4-fluorophenyl or 3-pyridyl; and
Q is diethoxyphosphoryl, isopropylsulphinyl, methylsulphonyl, isopropylsulphonyl, phenylsulphonyl, benzylsulphonyl, 4-pyridylsulphonyl, N-methylsulphamoyl, N,N-dimethylsulphamoyl or morpholinosulphonyl;
or a pharmaceutically-acceptable salt thereof.

A specific especially preferred quinazoline derivative of the invention includes, for example, the following quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof:-

4-[N-(2-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin,
4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin or
N,N-dimethyl-α-{p-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl}-α-toluenesulphonamide.

A further specific especially preferred quinazoline

derivative of the invention includes, for example, the following quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof:-

4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-isopropylsulphonyldesoxybenzoin,

N,N-dimethyl-p-fluoro-α-{p-[N-(2,7-dimethyl-4-oxo-3,4-dihydro-quinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl}-α-toluenesulphonamide, 2,4′-difluoro-4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyl-desoxybenzoin, N,N-dimethyl-p-fluoro-α-{o-fluoro-p-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl}-α-toluenesulphonamide,

4′-fluoro-4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin,

2,4′-difluoro-4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-morpholinosulphonyldesoxybenzoin,

α-{5-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]pyridine-2-carbonyl}-p-fluoro-N,N-dimethyl-α-toluenesulphonamide or

4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]phenyl 1-methylsulphonyl-1-(3-pyridyl)methyl ketone.

A compound of the invention comprising a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of structurally-related compounds. Such procedures are provided as a further feature of the invention and are illusrated by the following representative examples in which, unless otherwise stated, R^1, R^2, Ar^1, Ar^2 and Q have any of the meanings defined hereinbefore, provided that, when there is an amino, alkylamino, piperazin-1-yl, hydroxy or carboxy group in R^1, R^2, Ar^1, Ar^2 or Q, any such group may optionally be protected by a conventional protecting group which may be removed when so desired by conventional means.

(a) The reaction of an acid of the formula II (set out hereinafter), or a reactive derivative thereof, wherein R^3 is hydrogen or a protecting group, with a compound of the formula Ar^2-CH_2-Q.

A suitable reactive derivative of an acid of the formula II is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol or an alcohol such as 1-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as dicyclohexylcarbodiimide.

The reaction is preferably carried out in the presence of a suitable base such as, for example, an alkali or alkaline earth metal carbonate, alkoxide, hydroxide or hydride, for example sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, or an organometallic base such as an alkyl-lithium, for example n-butyl-lithium, or a dialkylamino-lithium, for example lithium di-isopropylamide, or, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine or diazabicyclo-[5.4.0]undec-7-ene. The reaction is also preferably carried out in a suitable inert solvent or diluent, for example tetrahydrofuran, 1,2-dimethoxyethane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulphoxide or acetone, and at a temperature in the range, for example, -78° to $150^{\circ}C$, conveniently at or near ambient temperature.

A suitable value for R^3 when it is a protecting group is, for example, a pivaloyloxymethyl group which may be removed by hydrolysis with a base, for example sodium hydroxide or ammonia, in a suitable inert solvent or diluent, for example methanol or ethanol.

A suitable protecting group for an amino, alkylamino or piperazin-1-yl group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a

methoxycarbonyl, ethoxycarbonyl or tert-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a tert-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid such as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-charcoal, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-charcoal.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a tert-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a

catalyst such as palladium-on-charcoal.

The starting materials of the formula II and of the formula Ar^2-CH_2-Q may be prepared by standard procedures of organic chemistry. The preparation of examples of such starting materials is described within the accompanying non-limiting Examples which are provided for the purpose of illustration only. Other necessary starting materials are obtainable by analogous procedures to those described or by modifications thereto which are within the ordinary skill of an organic chemist. Thus, for example, the starting material of the formula II may be prepared by the reaction of a compound of the formula III wherein Z is a displaceable group, with an amine of the formula:

$$HNR^2\text{-}Ar^1\text{-}CO_2R^4$$

wherein R^4 is a protecting group which can be removed to provide a carboxylic acid.

A suitable value for the displaceable group Z is, for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, mesyloxy or 4-toluenesulphonyloxy group.

A suitable value for R^4 is, for example, an alkyl group such as a methyl or ethyl group which may be removed by hydrolysis with a base such as sodium hydroxide, or R^4 is a <u>tert</u>-butyl group which may be removed by cleavage with an acid, for example an organic acid such as trifluoroacetic acid. The protecting group R^4 may be, for example an esterifying group which can be removed while the protecting group for any amino, alkylamino, hydroxy or carboxy group in R^1, R^2 and Ar^1 is retained.

(b) The reaction of a compound of the formula III wherein R^3 and Z have the meanings defined above, with an amine of the formula:

$$HNR^2\text{-}Ar^1\text{-}CO\text{-}CH(Ar^2)(Q)$$

The reaction is preferably carried out in the presence of a suitable base as defined above, in a suitable inert solvent or diluent as defined above, and at a temperature in the range, for example 25°

to 150^{o}C, conveniently at or near 90^{o}C.

The starting materials of the formula III and of the formula:

$$HNR^{2}\text{-}Ar^{1}\text{-}CO\text{-}CH(Ar^{2})(Q)$$

may be prepared by standard procedures of organic chemistry. The preparation of examples of compounds of the formula III is described within the accompanying non-limiting Examples which are provided for the purpose of illustration only. Other necessary starting materials are obtainable by analogous procedures to those described or by modifications thereto which are within the ordinary skill of an organic chemist.

(c) For the production of a compound of the formula I wherein Q is a group which comprises a sulphinyl or sulphonyl group, the oxidation of the corresponding compound of the formula I wherein Q is a group which comprises a thio group.

A suitable oxidising agent is, for example, any agent known in the art for the oxidation of thio to sulphinyl and/or sulphony, for example, hydrogen peroxide, a peracid (such as 3-chloroperoxybenzoic or peroxyacetic acid), an alkali metal peroxysulphate (such as potassium peroxymonosulphate), chromium trioxide or gaseous oxygen in the presence of platinum. The oxidation is generally carried out under as mild conditions as possible and with the required stoichiometric amount of oxidising agent in order to reduce the risk of over oxidation and damage to other functional groups. In general the reaction is carried out in a suitable solvent or diluent such as methylene chloride, chloroform, acetone, tetrahydrofuran or tert-butyl methyl ether and at a temperature, for example, at or near ambient temperature, that is in the range 15^{o} to 35^{o}C. When a compound carrying a sulphinyl group is required a milder oxidising agent may also be used, for example sodium or potassium metaperiodate, conveniently in a polar solvent such as acetic acid or ethanol. It will be appreciated that when a compound of the formula I containing a sulphonyl group is required, it may be obtained by oxidation of the corresponding sulphinyl compound as well as of the corresponding thio

compound.

(d) For the production of a compound of the formula I wherein R^1 is amino-(1-4C)alkyl or substituted-amino-(1-4C)alkyl, the reaction of a compound of the formula I wherein R^1 is hydroxy-(1-4C)alkyl, or a reactive derivative thereof, with ammonia or a substituted-amine.

A suitable reactive derivative of a compound of the formula I wherein R^1 is hydroxy-(1-4C)alkyl is, for example, a compound of the formula I wherein R^1 is a halogeno-(1-4C)alkyl or sulphonyloxy-(1-4C)-alkyl group, for example a chloro-(1-4C)alkyl, mesyloxy-(1-4C)alkyl or a 4-toluenesulphonyloxy-(1-4C)alkyl group.

The reaction is preferably carried out in a suitable inert solvent or diluent, for example methanol, ethanol, tetrahydrofuran or N,N-dimethylformamide, and at a temperature in the range, for example, 0^o to 100^oC, conveniently at or near ambient temperature.

(e) For the production of a compound of the formula I wherein R^1 is (2-4C)alkanoyloxy-(1-4C)alkyl or substituted-(2-4C)alkanoyloxy-(1-4C)alkyl, the reaction, conveniently in the presence of a suitable base as defined hereinbefore, of a compound of the formula I wherein R^1 is hydroxy-(1-4C)alkyl with an acylating reagent.

A suitable acylating reagent is, for example, a (2-4C)alkanoyl or substituted (2-4C)alkanoyl halide (especially an appropriate alkanoyl chloride or bromide) or a corresponding anhydride.

The reaction is preferably carried out in a suitable inert solvent or diluent, for example methylene chloride, chloroform, tetrahydrofuran or N,N-dimethylformamide, and at a temperature in the range, for example, 0^o to 100^oC, conveniently at or near room temperature.

(f) For the production of a compound of the formula I wherein Q is a piperazin-1-ylsulphonyl group, the cleavage of a compound of the formula I wherein Q is a 4-(1-4C)alkoxycarbonylpiperazin-1-yl group.

The cleavage conditions for the removal of the (1-4C)alkoxycarbonyl group necessarily vary with the nature of the (1-4C)alkyl group therein. Thus, for example, a (1-4C)alkyl group such as methyl or ethyl may be removed by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium

hydroxide. Alternatively a (1-4C)alkyl group such as a tert-butyl group may be removed, for example, by treatment with a suitable acid such as hydrochloric, sulphuric, phosphoric or trifluoroacetic acid.

When a pharmaceutically-acceptable salt of a compound of the formula I is required, it may be obtained, for example, by reaction of said compound with a suitable acid or base using a conventional procedure. When an optically active form of a compound of the formula I is required, it may be obtained by carring out one of the aforesaid processes using an optically active starting material, or by resolution of a racemic form of said compound using a conventional procedure.

As stated above a quinazoline derivative of the present invention possesses anti-tumour activity. This activity may be assessed, for example, using one or more of the procedures set out below:-

(a) An *in vitro* assay which determines the ability of a test compound to inhibit the enzyme thymidylate synthase. Thymidylate synthase was obtained in partially purified form from L1210 mouse leukaemia cells and utilised using the procedures described by Jackman *et al*. (*Cancer Res*., 1986, *46*, 2810 and Sikora *et al*., *Biochem. Pharmacol*. 1988, 37, 4047);

(b) An assay which determines the ability of a test compound to inhibit the growth of the leukaemia cell line L1210 in cell culture. The test is similar to that described in UK Patent Specification No. 2065653B and has been described by Jones *et al*., *J. Med. Chem*., 1985, *28*, 1468;

(c) An assay which determines the ability of a test compound to inhibit the growth of the human breast cancer cell line MCF-7 in cell culture. The test is similar to that described by Lippman *et al*. (*Cancer Res*., 1976, *36*, 4595); and

(d) An assay which determines the ability of a test compound to be cytotoxic to the lymphoma cell line L5178Y TK-/- *in vitro*. The lymphoma cell line L5178Y TK-/- is deficient in the enzyme thymidine kinase which phosphorylates thymidine and thus operates to generate a pool of thymidylate when *de novo* synthesis of thymidylate is prevented by the presence of an effective amount of an

inhibitor of thymidylate synthase. The L5178Y TK-/- cell line is thereby more sensitive to the presence of an inhibitor of thymidylate synthase. [L5178Y TK-/- was obtained by mutation of the parent L5178Y cell line which is described by, for example, Fischer *et al.*, *Methods in Medical Research*, 1964, 10, 247].

Although the pharmacological properties of the quinazolines of the invention vary with structural changes, in general quinazolines of the invention possess activity in one or more of the above tests (a) to (d):-

Test (a) IC_{50} in the range, for example, 0.05-10 μM;
Test (b) IC_{50} in the range, for example, 0.1-20 μM;
Test (c) IC_{50} in the range, for example, 0.1-10 μM;
Test (d) IC_{50} in the range, for example, 0.05-10 μM.

In general those quinazolines of the invention which are especially preferred possess activity in one or more of the above tests (a) to (d):-

Test (a) IC_{50} in the range, for example, 0.05-2 μM;
Test (b) IC_{50} in the range, for example, 0.1-10 μM;
Test (c) IC_{50} in the range, for example, 0.1-5 μM;
Test (d) - IC_{50} in the range, for example, 0.05-2 μM.

Thus, by way of example, the compound 4-[N-(2-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin has an IC_{50} of ~0.4μM in Test (a), an IC_{50} of ~1.2μM in Test (b) and an IC_{50} of ~0.7μM in Test (c); the compound 4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin has an IC_{50} of ~0.07μM in Test (a), an IC_{50} of ~0.7μM in Test (b) and an IC_{50} of ~0.1μM in Test (c); and the compound N,N-dimethyl-α-{p-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl}-α-toluenesulphonamide has an IC_{50} of ~0.08μM in Test (a), an IC_{50} ~0.56 μM in Test (b) and an IC_{50} of ~0.3μM in Test (c).

A quinazoline derivative of the present invention may itself be active or it may be a pro-drug which is converted *in vivo* to an active compound.

A quinazoline derivative of the invention, or a pharmaceutically-acceptable salt thereof, may be administered to a

warm-blooded animal, including a human, in the form of a pharmaceutical composition which comprises the quinazoline derivative, or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use, for example a cream, ointment, gel or aqueous or oily solution or suspension; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder such as a dry powder, a microcrystalline form or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oily solution, emulsion or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The composition may contain, in addition to the quinazoline derivative of the invention, one or more other anti-tumour substances, for example those selected from, for example, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; other antimetabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example asparaginase; topoisomerase inhibitors, for example etoposide; and biological response modifiers, for example interferon.

The quinazoline will normally be administered to a warm-blooded animal at a unit dose within the range 50-5000 mg per square metre body area of the animal, i.e. approximately 1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example, 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner

who is treating any particular patient.

According to a further feature of the invention there is provided a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

According to a further feature of the present invention there is provided a method for producing an anti-tumour effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the present invention, or a pharmaceutically-acceptable salt thereof.

The invention also provides the use of a quinazoline derivative of the present invention, or a pharmaceutically-acceptable salt thereof, in the manufacture of a novel medicament for use in the production of an anti-tumour effect in a warm blooded animal, such as man.

A quinazoline of the present invention is expected to possess a wide range of anti-tumour activities. CB3717 showed promising activity against human breast, ovarian and liver cancer and consequently it is expected that a quinazoline of the present invention will possess anti-tumour activity against these cancers. It is in addition expected that a quinazoline of the present invention will possess anti-tumour activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas. Such tumours require thymidine monophosphate as one of the essential nucleotides for the synthesis of cellular DNA. In the presence of an effective amount of a thymidylate synthase inhibitor such as an effective amount of a quinazoline of the present invention it is expected that tumour growth will be inhibited.

As previously mentioned a quinazoline derivative of the invention, or a pharmaceutically-acceptable salt thereof, is also of value in the treatment of, for example, allergic conditions such as psoriasis. In using a quinazoline of the invention for this purpose the compound will normally be administered at a dose within the range 50-5000 mg per square metre body area of the animal. In general for the treatment of an allergic condition such as psoriasis topical

administration of a quinazoline of the invention is preferred. Thus, for example, for topical administration a daily dose in the range, for example, 1 to 50 mg/kg will be used.

The invention is illustrated but not limited by the following Examples in which unless otherwise stated:-

(i) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-20^{o}C and under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were preformed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 reverse-phase silica (Art. 9303) obtained from E. Merck, Darmstadt, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the end-products of the formula I have satisfactory microanalyses and their structures were confirmed by NMR and mass spectral techniques [proton magnetic resonance spectra were determined using a Jeol FX 90Q or a Bruker AM200 spectrometer operating at a field strength of 200 MHz; chemical shifts are reported in parts per million downfield from tetramethylsilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; d of d's, doublet of doublet's; t, triplet, m, multiplet; fast-atom bombardment (FAB) mass spectral data were obtained using a VG Analytical MS9 spectrometer and xenon gas and, where appropriate, either positive ion data or negative ion data were collected];

(vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, infra-red (IR) or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus, a Koffler hot plate apparatus or an oil-bath apparatus; and

(viii) the following abbreviations have been used:-

THF	tetrahydrofuran;
DMF	N,N-dimethylformamide;
DMA	N,N-dimethylacetamide.

Example 1

n-Butyl lithium (1.5M in hexane, 2.34ml) was added dropwise to a stirred solution of di-isopropylamine (0.355g) in THF (25ml) which had been cooled to -70°C and the mixture was stirred at -70°C for 10 minutes. A solution of ethyl p-tolylacetate (0.568g) in THF (5ml) was added and the mixture was stirred at -70°C for 30 minutes. A solution of pentafluorophenyl p-{N-[2-methyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}-benzoate (European Patent Application No. 0373891, Example 33 thereof; 1g) in THF (10ml) was added. The mixture was stirred at -70°C for 1 hour and at ambient temperature for 2 hours. The mixture was poured into 1N aqueous hydrochloric acid solution and extracted with ethyl acetate (3 x 25ml). The combined extracts were washed with water (3 x 20ml) and with brine, dried ($MgSO_4$) and evaporated to leave a yellow oil. The acidity of the aqueous layer was reduced to pH5 by the addition of 1N aqueous sodium carbonate solution. The precipitate so obtained was isolated, washed with water and dried. The yellow oil and solid so obtained were combined and purified by column chromatography using increasingly polar mixtures of ethyl acetate and ethanol to give ethyl 2-{p-[N-(2-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl}-2-(p-tolyl)acetate as a gum which on trituration under diethyl ether gave a white solid (0.239g, 27%), m.p. 124-126°C.

Elemental Analysis : Found C, 72.1; H, 5.6; N, 8.2;
$C_{31}H_{29}N_3O_4$ $0.5H_2O$ requires C, 72.1; H, 5.9; N, 8.2%.

Example 2

n-Butyl lithium (1.55M in hexane, 1.3ml) was added dropwise to a stirred solution of benzyl methyl sulphone (0.34g) in THF (47ml) which had been cooled to -70°C. The mixture was stirred at -70°C for 30 minutes. A solution of pentafluorophenyl p-{N-[2-methyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}benzoate (0.627g) in THF (3ml) was added. The mixture was stirred at -70°C for 1 hour and at ambient temperature for 16 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried ($MgSO_4$) and evaporated. The residue was purified by

column chromatography using increasingly polar mixtures of hexane and ethyl acetate as eluent. There was thus obtained a white foam which, on trituration under diethyl ether, gave 4-[N-(2-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin (0.187g, 37%), m.p. 144-147°C.

NMR Spectrum ($CDCl_3$ + CD_3SOCD_3) 2.46 (s, 3H), 2.51 (t, 1H), 3.01 (s, 3H), 4.24 (broad s, 2H), 4.78 (s, 2H), 6.20 (s, 1H), 6.8-7.5 (m, 5H), 7.6-8.0 (m, 6H), 8.04 (s, 1H).

Elemental Analysis: Found C, 64.1; H, 5.2; N, 7.8;
$C_{28}H_{25}N_3O_4S$ $1H_2O$ requires C, 64.4; H, 5.8; N, 8.1%.

Example 3

Phenylnitromethane [Acta Chem. Scand. Ser. B, 1979, 33, 208; 0.301g] was added to a mixture of pentafluorophenyl p-{N-[2-methyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}benzoate (0.627g), triethylamine (1.38ml) and DMF (10ml) and the mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was purified by column chromatography using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained 4-{N-[2-methyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}-α-nitrodesoxybenzoin (0.069g).

A mixture of the product so obtained and a saturated solution of ammonia in methanol (10ml) was stirred at ambient temperature for 48 hours. The mixture was evaporated and the residue was triturated under diethyl ether. There was thus obtained 4-[N-(2-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-nitrodesoxybenzoin (0.038g, 8%), m.p. 173-180°C.

NMR Spectrum (CD_3SOCD_3) 3.30 (t, 1H), 3.32 (s, 3H), 4.62 (d, 2H), 4.86 (s, 2H), 6.92 (d, 2H), 7.53 (t, 1H), 7.61 (m, 1H), 7.65 (d, 1H), 7.69 (m, 1H), 7.83 (d, 1H), 7.88 (d, 2H), 7.97 (d, 1H).

Elemental Analysis: Found C, 67.8; H, 5.1; N, 11.8;
$C_{27}H_{22}N_4O_4$ $0.5H_2O$ requires C, 68.1; H, 4.8; N, 11.7%.

Example 4

n-Butyl lithium (1.6M in hexane, 2.56ml) was added dropwise to a stirred solution of diethyl benzylphosphonate (0.912g) in THF (40ml) which had been cooled to -70°C. The mixture was stirred at -70°C for 5 minutes and at -40°C for 15 minutes. A solution of pentafluorophenyl p-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}benzoate (0.627g) in THF (10ml) was added and the mixture was stirred at -60°C for 15 minutes and at ambient temperature for 1 hour. The mixture was acidified by the addition of glacial acetic acid. The mixture was evaporated and the residue was purified by reverse-phase column chromatography using decreasing polar mixtures of water, methanol and trifluoroacetic acid as eluent. There was thus obtained α-diethoxyphosphoryl-4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]desoxybenzoin (0.148g, 26%), m.p. 190-196°C.

NMR Spectrum (CD_3SOCD_3) 1.09 (t, 6H), 2.36 (s, 3H), 2.44 (s, 3H), 3.19 (t, 1H), 3.86-4.01 (m, 4H), 4.32 (d, 2H), 4.72 (s, 2H), 5.61 (d, 1H), 6.77 (d, 2H), 7.21-7.38 (m, 3H), 7.45 (s, 1H), 7.52-7.59 (m, 2H), 7.67 (s, 1H), 7.92 (d, 2H).

Elemental Analysis : Found C, 58.8; H, 5.4; N, 6.5; $C_{32}H_{34}N_3O_5P$ $0.5CF_3CO_2H$ requires C, 59.2; H, 5.8; N, 6.2%.

The pentafluorophenyl p-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)-amino}benzoate used as a starting material was obtained as follows:-

2,6,7-Trimethyl-3,4-dihydroquinazolin-4-one (European Patent Specification No. 0284338) was reacted with chloromethyl pivalate using the procedure described in European Patent Specification No. 0239362 for the corresponding reaction of 2,6-dimethyl-3,4-dihydroquinazolin-4-one. There was thus obtained 3-(pivaloyloxymethyl)-2,6,7-trimethyl-3,4-dihydroquinazolin-4-one. The product so obtained was reacted with N-bromosuccinimide in the presence of benzoyl peroxide using the procedure described in European Patent Specification No. 0284338 to give 6-bromomethyl-2,7-dimethyl-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-4-one in 57% yield, m.p. 149-152°C.

The product so obtained was reacted with tert-butyl p-(prop-2-ynyl)aminobenzoate using an analogous procedure to that described in European Patent Application No. 0239362 to give p-[N-(2,7-dimethyl-4-oxo-3-pivaloyloxymethyl-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid in 70% yield, m.p. 226°C (decomposes).

The product so obtained was reacted with pentafluorophenol using an analogous procedure to that described in European Patent Application No. 0373891 for the corresponding 7-H compound. There was thus obtained the required starting material in 69% yield, m.p. 168-171°C.

Example 5

n-Butyl lithium (1.6M in hexane, 0.79ml) was added dropwise to a stirred solution of benzyl methyl sulphone (0.216g) in THF (15ml) which had been cooled to -70°C. The mixture was stirred at -70°C for 30 minutes. A solution of pentafluorophenyl o-fluoro-p-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}benzoate (0.4g) in THF (5ml) was added. The mixture was stirred at -70°C for 30 minutes and at ambient temperature for 16 hours. The mixture was evaporated and the residue was purified by column chromatography using a 1:1 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 2-fluoro-4-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}-α-methylsulphonyl-desoxybenzoin (0.185g).

A mixture of the product so obtained and a saturated solution of ammonia in methanol (10ml) was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was purified by reverse phase column chromatography using decreasingly polar mixtures of water, methanol and trifluoroacetic acid as eluent. There was thus obtained 2-fluoro-4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyl-desoxybenzoin (0.061g, 40%), m.p. 143-156°C.

NMR Spectrum (CD_3SOCD_3) 2.34 (s, 3H), 2.41 (s, 3H), 2.97 (s, 3H), 3.21 (t, 1H), 4.33 (d, 2H), 4.74 (s, 2H), 6.21 (s, 1H), 6.58 (m, 1H), 6.67

(m, 1H), 7.36-7.62 (m, 8H), 7.61 (t, 1H).

Elemental Analysis: Found C, 56.2; H, 4.2; N, 6.2; $C_{29}H_{26}FN_3O_4S$ 1.2CF_3CO_2H requires C, 56.4, H, 4.1; N, 6.3%.

The pentafluorophenyl o-fluoro-p-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)-amino}benzoate used as a starting material was obtained as follows:-

A mixture of 6-bromomethyl-2,7-dimethyl-3-(pivaloyloxy-methyl)-3,4-dihydroquinazolin-4-one (0.9g), tert-butyl-o-fluoro-p-(prop-2-ynyl)aminobenzoate [0.882g; prepared in 56% yield by the reaction of tert-butyl p-amino-o-fluorobenzoate (European Patent Application No. 0373891) with propargyl bromide], potassium carbonate (0.691g), 18-crown-6 (0.005g) and N-methylpyrrolidin-2-one (20ml) was stirred and heated to 90°C for 6 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent.

A mixture of the product so obtained (0.9g) and trifluoro-acetic acid (20ml) was stirred at ambient temperature for 1 hour. The mixture was evaporated and the residue was triturated under diethyl ether. There was thus obtained o-fluoro-p-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}benzoic acid as a solid (0.64g).

Elemental Analysis Found C, 64.7; H, 5.5; N, 8.2; $C_{27}H_{28}FN_3O_5$ 0.1CF_3CO_2H requires C, 64.7; H, 5.6; N, 8.3%.

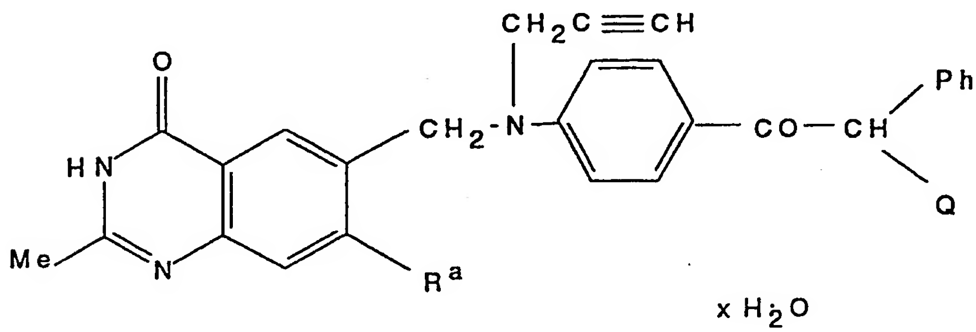
The product so obtained was reacted with pentafluorophenol using an analogous procedure to that described in European Patent Application No. 0373891 for the corresponding o-H, 7-H compound. There was thus obtained the required starting material in 42% yield, m.p. 170-171°C.

Example 6

Using an analogous procedure to that described in Example 2, except that, where necessary, the appropriate pentafluorophenyl benzoate was used in place of pentafluorophenyl p-{N-[2-methyl-4-oxo-

3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}benzoate and the appropriate nucleophile was used in place of benzyl methyl sulphone there were obtained the quinazoline derivatives described in the following Table, the structures of which were confirmed by proton magnetic resonance and mass spectroscopy and by elemental analysis.

TABLE I



Example 6 Compound No.	R[a]	Q	x	m.p. (°C)
1[a]	H	cyano	-	113-115
2	Me	methylsulphonyl	0.5	236-242
3[b]	Me	isopropylsulphinyl	0.5	190-194
4[c]	Me	isopropylsulphonyl	0.2	262-265
5[d]	Me	benzylsulphonyl	0.7	279-281
6[e]	H	N,N-dimethylsulphamoyl	0.4	122-124
7[e,f]	Me	N,N-dimethylsulphamoyl	-	143-151
8[g]	Me	N-methylsulphamoyl	-	134-153
9[h]	Me	morpholinosulphonyl	0.5	166-170

Notes

a. The product was purified by reverse-phase chromatography using decreasingly polar mixtures of water, methanol and trifluoroacetic acid as eluent. The product so obtained contained

1.35 equivalents of trifluoroacetic acid.

b. The benzyl isopropyl sulphoxide used as a starting material was obtained as follows:-

α-Toluenethiol (12.4g) was added to a solution of sodium ethoxide [obtained by the addition of sodium (2.3g) to ethanol (200ml)] and the mixture was stirred at ambient temperature for 5 minutes. Isopropyl bromide (12.3g) was added and the mixture was stirred at ambient temperature for 2 days. The mixture was evaporated and the residue was partitioned between ethyl acetate and 2N aqueous sodium hydroxide solution. The organic phase was washed with 2N aqueous sodium hydroxide solution and with water, dried ($MgSO_4$) and evaporated. There was thus obtained benzyl isopropyl sulphide (22.1g).

A mixture of a portion (12.3g) of the product so obtained, 3-chloroperoxybenzoic acid (12.7g) and methylene chloride (500ml) was stirred at at 0°C for 15 minutes and at ambient temperature for 2 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography using a 7:3 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained the required starting material (8.8g) as a solid.

c. The benzyl isopropyl sulphone used as the appropriate nucleophile was obtained as follows:-

A mixture of benzyl isopropyl sulphoxide (5g), 3-chloroperoxybenzoic acid (6.3g) and methylene chloride (100ml) was stirred at 0°C for 15 minutes and at ambient temperature for 4 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography using methylene chloride as eluent. There was thus obtained the required starting material (4.1g, 75%), m.p. 65-66°C.

d. Lithium di-isopropylamide (prepared as described in Example 1) was used in place of n-butyl lithium to generate the lithium salt of dibenzyl sulphone.

The dibenzyl sulphone starting material was obtained as follows:-

Benzyl bromide (11.96ml) was added to a solution of α-toluenethiol (12.4g) in 2N aqueous sodium hydroxide solution

(100ml) and the mixture was stirred vigorously for 3 days at ambient temperature. The mixture was partitioned between ethyl acetate and water. The organic phase was washed with 2N aqueous sodium hydroxide solution and with water, dried ($MgSO_4$) and evaporated. There was thus obtained dibenzyl sulphide (22g).

A mixture of the product so obtained, 3-chloroperoxybenzoic acid (32.2g) and methylene chloride (400ml) was stirred at at 0°C for 15 minutes and at ambient temperature for 3 hours. The mixture was filtered and the filtrate was washed with 2N aqueous sodium hydroxide solution, with water, with 2N aqueous hydrochloric acid and with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using methylene chloride as eluent. There was thus obtained the required starting material (12.1g), m.p. 148-149°C.

e. Lithium di-isopropylamide (2.2 equivalents) was used in place of n-butyl lithium to generate the lithium salt of N,N-dimethyl-α-toluenesulphonamide.

The N,N-dimethyl-α-toluenesulphonamide used as a starting material was obtained as follows:-

A solution of α-toluenesulphonyl chloride (8.64g) in methylene chloride (20ml) was added dropwise to a vigorously stirred mixture of a 40% w/v solution of dimethylamine in water (80ml) and methylene chloride (100ml) which had been cooled to 0°C. The mixture was stirred at ambient temperature for 2 hours. The organic layer was separated, dried ($MgSO_4$) and evaporated. The resultant solid was recrystallised from a 10:2:1 mixture of toluene, hexane and ethanol. There was thus obtained the required starting material (5.84g, 65%), m.p. 98-100°C.

f. The product of the standard procedure was further purified by reverse-phase column chromatography using decreasingly polar mixtures of water, methanol and trifluoroacetic acid as eluent. There was thus obtained the required product in 10% yield, which was shown by elemental analysis to be carrying 1.1 equivalents of trifluoroacetic acid:-

Found C, 57.5; H, 5.1; N, 8.4;

$C_{30}H_{30}N_4O_4S$ 1.1CF_3CO_2H requires C, 57.8; H, 4.7; N, 8.4%.

g. Three equivalents of the lithium salt of N-methyl-$\underline{\alpha}$-toluenesulphonamide were used. The product of the standard work-up procedure was further purified by reverse-phase column chromatography using decreasingly polar mixtures of water, methanol and trifluoroacetic acid as eluent. There was thus obtained the required product in 10% yield, which was shown by elemental analysis to be carrying 1.45 equivalents of trifluoroacetic acid:-

Found C, 54.9; H, 4.6; N, 8.1;

$C_{29}H_{28}N_4O_4S$ $1.45CF_3CO_2H$ requires C, 55.2; H, 4.2; N, 8.1%.

The $\underline{N}$-methyl-$\underline{\alpha}$-toluenesulphonamide used as a starting material was obtained as follows:-

A solution of $\underline{\alpha}$-toluenesulphonyl chloride (3.59g) in methylene chloride (50ml) was added dropwise to a stirred mixture of a 33% w/v solution of methylamine in ethanol (20ml) and methylene chloride (200ml) which had been cooled to 5°C. The mixture was stirred at ambient temperature for 16 hours. The mixture was poured into water (200ml). The organic phase was washed with water and with brine, dried ($MgSO_4$) and evaporated. The resultant solid was recrystallised from a 4:1 mixture of hexane and ethyl acetate. There was thus obtained the required starting material (1.49g).

NMR Spectrum 2.69 (d, 3H), 4.10 (broad s, 1H), 4.25 (s, 2H), 7.39 (s, 5H).

h. Three equivalents of the lithium salt of benzyl morpholino sulphone were used, the salt being prepared by the addition of n-butyl lithium to a solution of the sulphone in THF which had been cooled to -20°C. The mixture was stirred at -10° to -20°C for 15 minutes and then cooled to -60°C prior to the addition of the appropriate pentafluorophenyl ester.

The benzyl morpholino sulphone used as a starting material was obtained as follows:-

A solution of a mixture of morpholine (1.64g) and pyridine (1.49g) in methylene chloride (30ml) was added dropwise to a stirred solution of $\underline{\alpha}$-toluenesulphonyl choride (3.59g) in methylene chloride (50ml). The mixture was stirred at ambient temperature for 72 hours. The mixture was washed in turn with water, with 2N aqueous hydrochloric acid and with water, dried ($MgSO_4$) and evaporated.

There was thus obtained the required sulphone (3.42g, 75%), m.p. 172-173°C (recrystallised from a 8:1 mixture of toluene and ethyl acetate).

Example 7

Using an analogous procedure to that described in Example 5, except that lithium di-isopropylamide (prepared as described in Example 1) was used in place of n-butyl lithium, benzyl phenyl sulphone (0.487g) was reacted with pentafluorophenyl p-{N-[2-methyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}benzoate (0.627g) to give 4-{N-[2-methyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}-α-phenylsulphonyldesoxybenzoin (0.295g).

Using an analogous procedure to that described in the second paragraph of Example 5, the pivaloyloxymethyl protecting group was removed from a portion (0.28g) of the material so obtained. There was thus obtained 4-[N-(2-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-phenylsulphonyldesoxybenzoin (0.166g), m.p. 141-151°C.

NMR Spectrum (CD_3SOCD_3) 2.36 (s, 3H), 3.18 (t, 1H), 4.36 (t, 2H), 4.81 (s, 2H), 6.7-8.0 (m, 17H).

Elemental Analysis : Found C, 61.9; H, 4.3; N, 6.1;
$C_{33}H_{27}N_3O_4S$ 1.1CF_3CO_2H requires C, 61.5; H, 4.1; N, 6.1%.

The benzyl phenyl sulphone used as a starting material was obtained as follows:-

A mixture of benzyl phenyl sulphide (10g), 3-chloroperoxybenzoic acid (17.3g) and methylene chloride (300ml) was stirred at 0°C for 20 minutes and at ambient temperature for 4 hours. The mixture was extracted with 2N aqueous sodium hydroxide solution and with water. The organic phase was dried ($MgSO_4$) and evaporated. The solid residue was recrystallised from a mixture of hexane and ethyl acetate. There was thus obtained the required starting material (8.6g), m.p. 145-146°C.

Example 8

The procedure described in Example 2 was repeated except

that methyl 3-nitrobenzyl sulphone was used in place of benzyl methyl sulphone. There was thus obtained 4-[N-(2-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyl-3'-nitrodesoxybenzoin in 14% yield, m.p. 140-146°C.

NMR Spectrum (CD_3SOCD_3) 2.36 (s, 3H), 2.97 (s, 3H), 3.05 (t, 1H), 4.42 (s, 2H), 4.87 (s, 2H), 6.8-8.65 (m, 11H).

Elemental Analysis : Found C, 59.8; H, 4.6; N, 8.8;

$C_{28}H_{24}N_4O_6S$ $0.6Et_2O$. 0.4NaCl requires C, 59.7; H, 4.9; N, 9.2%.

The methyl 3-nitrobenzyl sulphone used as a starting material was obtained as follows:-

3-Nitrobenzyl bromide (5.41g) was added portionwise to a stirred solution of sodium methanethiolate (1.94g) in DMF (20ml) and the mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to give methyl 3-nitrobenzyl sulphide (3.96g).

A solution of a portion (1.88g) of the sulphide so produced in methylene chloride (50ml) was added dropwise to a stirred solution of 3-chloroperoxybenzoic acid (7.44g) in methylene chloride (100ml) which had been cooled to 0°C. The mixture was stirred at ambient temperature for 16 hours. The mixture was washed with a saturated aqueous sodium bicarbonate solution, with a saturated aqueous sodium metabisulphite solution and with water, dried ($MgSO_4$) and evaporated. There was thus obtained methyl 3-nitrobenzyl sulphone (2.05g, 93%), as an oil which was used without further purification.

Example 9

n-Butyl lithium (1.6M in hexane, 1.68ml) was added dropwise to a stirred solution of N,N-dimethyl-α-toluenesulphonamide (0.577g) in THF (20ml) which had been cooled to -70°C. The mixture was allowed to warm to -40°C and was stirred for 15 minutes. The mixture was recooled to -70°C and a solution of pentafluorophenyl p-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-methylamino}benzoate (0.4g) in THF (4ml) was added. The mixture was stirred at -70°C for 30 minutes and at ambient temperature for 4 hours. The mixture was evaporated and the residue was purified

by column chromatography using increasingly polar mixtures of ethyl acetate and methanol as eluent. There was thus obtained N,N-dimethyl-α-{p-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-methylamino]benzoyl}-α-toluenesulphonamide (0.135g, 39%), m.p. 215-226°C.

NMR Spectrum (CD_3SOCD_3) 2.29 (s, 3H), 2.41 (s, 3H), 2.60 (s, 6H), 3.16 (s, 3H), 4.72 (s, 2H), 6.53 (s, 1H), 6.71 (d, 2H), 7.36 (m, 3H), 7.42 (s, 1H), 7.48 (s, 1H), 7.71 (m, 2H), 7.93 (d, 2H).

The pentafluorophenyl p-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-methylamino}-benzoate used as a starting material was obtained as follows:-

A mixture of 6-bromomethyl-2,7-dimethyl-3-(pivaloyloxy-methyl)-3,4-dihydroquinazolin-4-one (12g), p-methylaminobenzoic acid (5.4g), 2,6-lutidine (5g), sodium iodide (5mg) and DMF (175ml) was stirred and heated to 60°C for 20 hours. The mixture was cooled and partitioned between diethyl ether and water. The organic phase was washed with water and with brine, dried ($MgSO_4$) and evaporated. There was thus obtained a light brown solid (16.6g) which was used without further purification.

Pentafluorophenol (19.6g) and dicyclohexylcarbodiimide (16.5g) were added in turn to a solution of the product so obtained (16g) in DMF (380ml) which has been cooled in an ice-bath. The mixture was stirred at ambient temperature for 40 hours. The mixture was evaporated and the residue was purified by chromatography on silica gel using a 98.5:1.5 mixture of chloroform and methanol as eluent. There was thus obtained a light brown solid which was triturated under diethyl ether to give the required starting material (13.55g).

Example 10

n-Butyl lithium (1.5M in hexane, 2.8ml) was added dropwise to a stirred solution of p-fluorobenzyl morpholino sulphone (1g) in THF (40ml) which had been cooled to -40°C. The mixture was stirred at -40°C for 30 minutes. A solution of pentafluorophenyl p-[N-(2-acetoxymethyl-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-fluorobenzoate (0.36g) in THF (25ml) was added.

The mixture was stirred for 1 hour and allowed to warm to ambient temperature. Glacial acetic acid (2ml) was added. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography using a 20:1 mixture of ethyl acetate and methanol as eluent. There was thus obtained 2,4′-difluoro-4-[N-(2-hydroxymethyl-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-morpholinosulphonyldesoxybenzoin (0.3g, 78%), m.p. 120-122°C.

NMR Spectrum ($CDCl_3$) 2.32 (t, 1H), 2.44 (s, 3H), 3.16 (m, 4H), 3.58 (m, 4H), 4.13 (broad s, 2H), 4.63 (s, 2H), 4.68 (s, 2H), 6.05 (d, 1H), 6.37 (d of d's, 1H), 6.59 (d of d's, 1H), 7.0-8.0 (m, 7H).

Elemental Analysis: Found C, 58.5; H, 5.0; N, 8.3;

$C_{32}H_{30}F_2N_4O_6S$ $1H_2O$ requires C, 58.7; H, 4.9; N, 8.5%.

The pentafluorophenyl p-[N-(2-acetoxymethyl-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-fluorobenzoate used as a starting material was obtained as follows:-

A solution of methyl chloroacetimidate in methanol [obtained by the addition of sodium (0.2g) to a mixture of chloroacetonitrile (21ml) and methanol (250ml)] was added to a mixture of 4,5-dimethylanthranilic acid hydrochloride (60g; Acta. Chem. Scand., 21, 983) and sodium methoxide solution [obtained by the addition of sodium (7g) to methanol (400ml)]. The mixture was stirred and heated to reflux for 1 hour. The mixture was allowed to cool to ambient temperature. The precipitate was isolated and washed with methanol (500ml) and with water (500ml). There was thus obtained 2-chloromethyl-6,7-dimethyl-3,4-dihydroquinazolin-4-one (90g).

NMR Spectrum (CD_3SOCD_3) 2.37 (s, 6H), 4.53 (s, 2H), 7.46 (s, 1H), 7.86 (s, 1H).

A mixture of the product so obtained, sodium acetate (120g) and DMF (600ml) was stirred and heated to 80°C for 15 minutes. The mixture was cooled to ambient temperature and poured onto ice (1.5kg). The mixture was stirred for 20 minutes. The precipitate was isolated and dried. There was thus obtained 2-acetoxymethyl-6,7-dimethyl-3,4-dihydroquinazolin-4-one (46g).

NMR Spectrum (CD_3SOCD_3) 2.14 (s, 3H), 2.36 (s, 6H), 4.93 (s, 2H), 7.43 (s, 1H), 7.85 (s, 1H).

A mixture of a portion (26g) of the material so obtained, N-bromosuccinimide (20g), azobisisobutyronitrile (1.2g), chloroform (500ml) and carbon tetrachloride (1000ml) was stirred and heated to reflux while being irradiated with the light from a 300 watt lamp. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated to give 2-acetoxymethyl-6-bromomethyl-7-methyl-3,4-dihydroquinazolin-4-one (27g) which was used without further purification.

The product so obtained was reacted with tert-butyl o-fluoro-p-(prop-2-ynyl)aminobenzoate using analogous procedures to those described in the portion of Example 13 below which is concerned with the preparation of starting materials. There was thus obtained pentafluorophenyl p-[N-(2-acetoxymethyl-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-fluorobenzoate.
NMR Spectrum ($CDCl_3$ + CD_3SOCD_3) 2.20 (s, 3H), 2.49 (s, 3H), 2.58 (t, 1H), 4.20 (s, 2H), 4.70 (s, 2H), 5.32 (s, 2H), 6.60 (m, 2H), 7.34 (s, 1H), 7.58 (s, 1H), 7.96 (t, 1H).

The p-fluorobenzyl morpholino sulphone used as a starting material was obtained as follows:-

A solution of (4-fluorophenyl)methanesulphonyl chloride (J.Pharm.Sci., 64, 1961; 10.4g) in methylene chloride (50ml) was added dropwise to a stirred solution of morpholine (9.6g) in methylene chloride (30ml) which had been cooled to 5°C. The mixture was stirred at ambient temperature for 1 hour. The mixture was washed with 2N aqueous hydrochloric acid and with water, dried ($MgSO_4$) and evaporated. There was thus obtained the required starting material (12g, 92%), m.p. 158-159°C (recrystallised from a 1:1 mixture of hexane and ethyl acetate).

Example 11

Thionyl chloride (0.2ml) was added dropwise to a stirred solution of 2,4'-difluoro-4-[N-(2-hydroxymethyl-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-morpholinosulphonyldesoxybenzoin (0.2g) in methylene chloride (10ml). The mixture was stirred at ambient temperature for 3 hours. The mixture was evaporated and the residue was dissolved in a solution of

dimethylamine in methanol (30% w/v, 10ml). The solution was stirred at ambient temperature for 1 hour. The mixture was evaporated and the residue was purified by column chromatography using a 20:1 mixture of chloroform and methanol as eluent. There was thus obtained 2,4'-difluoro-4-[N-(2-dimethylaminomethyl-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-morpholinosulphonyl-desoxybenzoin (0.1g, 49%), m.p. 120°C.

NMR Spectrum ($CDCl_3$) 2.30 (t, 1H), 2.42 (s, 6H), 2.46 (s, 3H), 3.18 (m, 4H), 3.58 (m, 6H), 4.13 (d, 2H), 4.63 (s, 2H), 6.05 (d, 1H), 6.37 (d of d's, 1H), 6.60 (d of d's, 1H), 7.0-8.0 (m, 7H).

Elemental Analysis: Found C, 60.2; H, 5.4; N, 10.1;

$C_{34}H_{35}F_2N_5O_5S$ $1H_2O$ requires C, 59.9; H, 5.4; N, 10.3%.

Example 12

The procedure described in Example 10 was repeated except that benzyl methyl sulphone was used in place of p-fluorobenzyl morpholino sulphone and that the reaction mixture was cooled initially to -50°C for the addition of the n-butyl lithium, warmed to -10°C during 30 minutes after the addition of the n-butyl lithium and recooled to -50°C for the addition of the benzoate. There was thus obtained 2-fluoro-4-[N-(2-hydroxymethyl-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyl-desoxybenzoin in 98% yield, m.p. 203-205°C.

NMR Spectrum (CD_3SOCD_3) 2.35 (t, 1H), 2.44 (s, 3H), 3.0 (s, 3H), 4.15 (d, 2H), 4.58 (s, 2H), 4.65 (s, 2H), 5.87 (d, 1H), 6.36 (d of d's, 1H), 6.62 (d of d's, 1H), 7.4-7.9 (m, 8H).

Elemental Analysis: Found C, 61.5; H, 4.6; N, 7.3;

$C_{29}H_{26}FN_3O_5S$ $1H_2O$ requires C, 61.6; H, 4.9; N, 7.4%.

Example 13

Using an analogous procedure to that described in Example 12, pentafluorophenyl p-[N-(2-acetoxymethyl-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoate was reacted with benzyl methyl sulphone to give 4-[N-(2-hydroxymethyl-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)-amino]-α-methylsulphonyldesoxybenzoin in 25% yield, m.p. 150°C.

NMR Spectrum (CD_3SOCD_3) 2.43 (s, 3H), 2.96 (s, 3H), 3.19 (t, 1H), 4.33 (m, 4H), 4.73 (s, 2H), 6.61 (s, 1H), 6.80 (d, 2H), 7.4-8.0 (m, 9H).
Elemental Analysis: Found C, 63.4; H, 5.3; N, 7.6;
$C_{29}H_{27}N_3O_5S$ $1H_2O$ requires C, 63.6; H, 5.3; N, 7.7%.

The pentafluorophenyl p-[N-(2-acetoxymethyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoate used as a starting material was obtained as follows:-

A mixture of 2-acetoxymethyl-6-bromomethyl-7-methyl-3,4-dihydroquinazolin-4-one (27g), tert-butyl-p-(prop-2-ynyl)-aminobenzoate (16g), powdered calcium carbonate (10g) and DMF (200ml) was stirred and heated to 90°C for 16 hours. The hot mixture was filtered and the filtrate was evaporated. The residue was triturated under methylene chloride to give tert-butyl p-[N-(2-acetoxy-methyl-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoate (20g).
NMR Spectrum (CD_3SOCD_3) 1.51 (s, 9H), 2.12 (s, 3H), 2.46 (s, 3H), 3.18 (t, 1H), 4.31 (d, 2H), 4.71 (s, 2H), 4.92 (s, 2H), 6.80 (d, 2H), 7.50 (s, 1H), 7.72 (d, 2H), 7.75 (s, 1H).

A mixture of a portion (8g) of the material so obtained, trifluoroacetic acid (50ml) and methylene chloride (50ml) was stirred at ambient temperature for 3 hours. The mixture was evaporated and the residue was triturated under diethyl ether. There was thus obtained p-[N-(2-acetoxymethyl-7-methyl-4-oxo-3,4-dihydro-quinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid (7.4g).

A mixture of the product so obtained, pentafluorophenol (9g), dicyclohexylcarbodiimide (12g), 4-dimethylaminopyridine (1g) and DMF (100ml) was stirred at ambient temperature for 16 hours. The mixture was filtered and the filtrate was evaporated. The residue was triturated under a 4:1 mixture of chloroform and acetone. There was thus obtained pentafluorophenyl p-[N-(2-acetoxymethyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoate (7.3g).
NMR Spectrum (CD_3SOCD_3) 2.13 (s, 3H), 2.46 (s, 3H), 3.25 (t, 1H), 4.41 (d, 2H), 4.81 (s, 2H), 4.93 (s, 2H), 6.95 (d, 2H), 7.53 (s, 1H), 7.73 (s, 1H), 7.99 (d, 2H).

Example 14

Using an analogous procedure to that described in Example 11, 4-[N-(2-hydroxymethyl-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino-α-methylsulphonyldesoxybenzoin was reacted in turn with thionyl chloride and N-methylpiperazine to give 4-{N-[7-methyl-2-(4-methylpiperazin-1-ylmethyl)-4-oxo-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}-α-methylsulphonyldesoxybenzoin in 45% yield, m.p. 170°C.

NMR Spectrum (CD_3SOCD_3) 2.24 (s, 3H), 2.44 (s, 3H), 2.97 (s, 3H), 3.19 (t, 1H), 3.26 (m, 8H), 3.40 (s, 2H), 4.34 (s, 2H), 4.73 (s, 2H), 6.61 (s, 1H), 6.80 (d, 2H), 7.6-8.0 (m, 9H).

Elemental Analysis: Found C, 64.8; H, 6.3; N, 11.0;
$C_{34}H_{37}N_5O_4S$ $1H_2O$ requires C, 64.9; H, 6.2; N, 11.1%.

Example 15

A mixture of 4-[N-(2-hydroxymethyl-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino-α-methylsulphonyldesoxybenzoin (0.2g), succinic anhydride (0.1g), triethylamine (0.15g) and chloroform (50ml) was stirred at ambient temperature for 2 hours. Glacial acetic acid (0.5ml) was added and the mixture was evaporated. The residue was purified by column chromatography using a 4:1 mixture of chloroform and methanol as eluent. The solid so obtained was dissolved in a 1:1 mixture of methanol and water (50ml) and brought to pH6 by the addition of 0.1N aqueous soidum bicarbonate solution. The precipitate was isolated and dried. There was thus obtained the sodium salt of 4-{N-[2-(3-carboxypropionyloxymethyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}-α-methylsulphonyldesoxybenzoin (0.11g, 36%).

NMR Spectrum (CD_3SOCD_3) 2.4-2.6 (m, 7H), 2.97 (s, 3H), 4.33 (s, 2H), 4.75 (s, 2H), 4.98 (s, 2H), 6.63 (s, 1H), 6.80 (d, 2H), 7.4-7.9 (m, 9H).

Elemental Analysis: Found C, 56.0; H, 5.2; N, 5.8;
$C_{33}H_{30}N_3O_8SNa$ $3H_2O$ requires C, 56.2; H, 5.1; N, 6.0%.

Example 16

A solution of p-fluorobenzyl morpholino sulphone (0.43g) in THF (10ml) was added dropwise to a stirred solution of lithium di-isopropylamide (2M in THF; 0.95ml) in THF (30ml) which had been cooled to -60°C. The mixture was stirred and allowed to warm to -20°C during 15 minutes. The mixture was recooled to -60°C and a solution of pentafluorophenyl o-fluoro-p-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxy-methyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}-benzoate (0.36g) in THF (10ml) was added. The mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The mixture was poured into a saturated aqueous ammonium chloride solution and extracted with ethyl acetate (2x40ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using increasingly polar mixtures of ethyl acetate and methanol as eluent. The product so obtained was triturated under diethyl ether. There was thus obtained 2,4′-difluoro-4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-morpholinosulphonyldesoxybenzoin (0.175g, 51%), m.p. 195-197°C.

NMR Spectrum (CD_3SOCD_3 + CD_3CO_2D) 2.3 (s, 3H), 2.4 (s, 3H), 3.0 (m, 4H), 3.45 (m, 4H), 4.32 (s, 2H), 4.72 (s, 2H), 6.23 (d, 1H), 6.6 (m, 2H), 7.2 (t, 2H), 7.4 (s, 1H), 7.68 (m, 3H), 7.82 (t, 1H).

Elemental Analysis: Found C, 58.5; H, 4.6; N, 8.0;

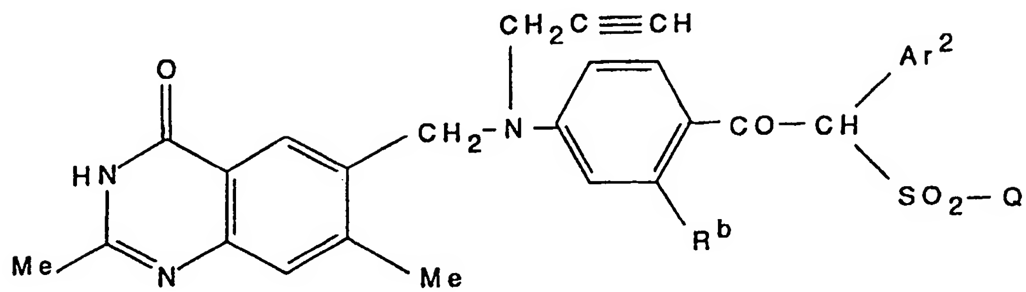
$C_{32}H_{30}F_2N_4O_5S$ 1HCl 0.2$(C_2H_5)_2O$ requires C, 58.6; H, 4.8; N, 8.3%.

Example 17

Using an analogous procedure to that described in Example 16, except that, where necessary, pentafluorophenyl p-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}benzoate was used in place of pentafluorophenyl o-fluoro-p-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxy-methyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}-benzoate and, where necessary, the appropriate sulphone was used in place of p-fluorobenzyl morpholino sulphone, there were obtained the quinazoline derivatives described in the following Table, the structures of which were confirmed by proton magnetic resonance and

mass spectroscopy and by elemental analysis.

TABLE II



Example 17 Compound No.	R^b	Ar^2	Q′	m.p. (°C)
1[a]	H	3-pyridyl	methyl	190-192
2[b]	F	p-fluorophenyl	methyl	171-173
3[c]	F	p-cyanophenyl	methyl	173-174
4[d]	F	p-fluorophenyl	4-pyridyl	198-199
5	H	p-fluorophenyl	methyl	163-166
6[e]	F	p-tolyl	methyl	-
7[f]	H	p-fluorophenyl	dimethylamino	163-165
8	H	p-fluorophenyl	morpholino	155-158
9[g]	F	p-fluorophenyl	N-(2-dimethyl-aminoethyl)-N-methylamino	134-135
10[h]	F	p-fluorophenyl	4-tert-butoxy-carbonyl-piperidin-1-yl	142-144
11[i]	F	2-pyridyl	methyl	-
12[j]	F	3-pyridyl	methyl	173-175

Notes

a. The product contained 1 equivalent of water.
The methyl 3-pyridylmethyl sulphone used as a starting

material was obtained as follows:-

Sodium methanethiolate (9.4g) was added to a stirred solution of 3-(chloromethyl)pyridine (10g) in DMF (50ml) and the mixture was stirred at ambient temperature for 2.5 hours. The mixture was partitioned between water and ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. There was thus obtained methyl 3-pyridylmethyl sulphide as an oil (5.9g, 70%).

NMR Spectrum ($CDCl_3$) 2.02 (s, 3H), 3.67 (s, 2H), 7.26 (m, 1H), 7.67 (m, 1H), 8.53 (m, 2H).

A solution of 3-chloroperoxybenzoic acid (13.5g) in methylene chloride (40ml) was added to a solution of methyl 3-pyridylmethyl sulphide (5.2g) in methylene chloride (40ml) which had been cooled to 0°C. The mixture was stirred at 0°C to 5°C for 1.5 hours. The mixture was evaporated. The residue was basified by the addition of a saturated aqueous sodium bicarbonate solution and the mixture was re-evaporated. The residue was triturated under methylene chloride. There was thus obtained methyl 3-pyridylmethyl sulphone (2.3g. 36%).

NMR Spectrum ($CDCl_3$ + CD_3SOCD_3) 2.97 (s, 3H), 4.58 (s, 2H), 7.46 (m, 1H), 7.83 (m, 1H), 8.59 (m, 2H).

b. n-Butyl lithium rather than lithium di-isopropylamide was used to generate the lithium salt of p-fluorophenyl methyl sulphone.

The product contained 0.2 equivalents of ethyl acetate.

The p-fluorobenzyl methyl sulphone used as a starting material was obtained from p-fluorobenzyl chloride using an analogous procedure to that described in Note a. above.

c. The p-cyanobenzyl methyl sulphone used as a starting material was obtained from p-cyanobenzyl bromide using an analogous procedure to that described in Note a. above.

d. The product contained 0.5 equivalents of water.

The p-fluorobenzyl 4-pyridyl sulphone used as a starting material was obtained as follows:-

4-Mercaptopyridine (1.7g) was added portionwise to a stirred mixture of sodium hydride (60% dispersion in mineral oil, 0.63g) and DMF (10ml) which had been cooled in an ice-bath. The mixture was stirred at 0°C for 10 minutes. p-Fluorobenzyl chloride (1g) was added

dropwise. The mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The mixture was partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using increasingly polar mixtures of hexane and ethyl acetate as eluent. There was thus obtained p-fluorobenzyl 4-pyridyl sulphide (1.1g, 72%).

NMR Spectrum ($CDCl_3$) 4.19 (s, 2H), 7.03 (m, 2H), 7.13 (d, 2H), 7.35 (m, 2H), 8.41 (broad s, 2H).

The material so obtained was oxidised with 3-chloroperoxybenzoic acid using an analogous procedure to that described in Note a. above. There was thus obtained p-fluorobenzyl 4-pyridyl sulphone.

NMR Spectrum (CD_3SOCD_3) 4.85 (s, 2H), 7.21 (m, 4H), 7.7 (m, 2H), 8.87 (m, 2H).

e. The methyl p-tolyl sulphone used as a starting material was obtained from p-tolyl chloride using an analogous procedure to that described in Note a. above.

f. The reaction mixture was maintained at 5°C for 16 hours rather than being allowed to warm to ambient temperature. The product contained 0.5 equivalents of water and 1 equivalent of $(C_2H_5)_2O$.

The p-fluoro-N,N-dimethyl-α-toluenesulphonamide used as a starting material was obtained as follows:-

A solution of (4-fluorophenyl)methanesulphonyl chloride (0.5g) in methylene chloride (10ml) was added to a stirred ethanolic solution of dimethylamine (33% in ethanol, 5ml) which had been cooled to 0°C. The mixture was allowed to warm to ambient temperature and was stirred for 2 hours. The mixture was evaporated and the residue was purified by column chromatography using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained p-fluoro-N,N-dimethyl-α-toluenesulphonamide (0.25g, 48%).

NMR Spectrum ($CDCl_3$) 2.78 (s, 6H), 4.18 (s, 2H), 7.09 (t, 2H), 7.38 (m, 2H).

g. The reaction mixture was maintained at -20°C for 20 minutes rather than being allowed to warm to ambient temperature for 16 hours.

The product contains 1 equivalent of water and 0.3 equivalents of ethyl acetate.

The p-fluoro-N-methyl-N-(2-dimethylaminoethyl)-α-toluene-sulphonamide used as a starting material was obtained by the reaction of (4-fluorophenyl)methanesulphonyl chloride and N-methyl-N-(2-dimethylaminoethyl)amine using an analogous procedure to that described in Note f. above.

h. The product contained 1 equivalent of water and 0.5 equivalents of ethyl acetate.

The p-fluorobenzyl 4-tert-butoxycarbonylpiperazin-1-yl sulphone used as a starting material was obtained by the reaction of (4-fluorophenyl)methanesulphonyl chloride and N-tert-butoxycarbonyl-piperazine using an analogous procedure to that described in Note f. above.

i. The product contained 0.5 equivalents of water and gave the following characteristic NMR data: (CD_3SOCD_3+CD_3CO_2D) 2.37 (s, 3H), 2.50 (s, 3H), 3.09 (s, 1H), 3.40 (s, 3H), 4.50 (s, 2H), 4.91 (s, 2H), 7.09 (t, 1H), 7.21 (d, 1H), 7.51 (d, 2H), 7.70 (m, 1H), 7.82 (s, 1H), 8.24 (d, 1H), 8.99 (d, 1H), 9.14 (d, 1H).

The methyl 2-pyridylmethyl sulphone used as a starting material was obtained from 2-(chloromethyl)pyridine using an analogous procedure to that described in Note a. above.

j. n-Butyl lithium rather than lithium di-isopropylamide was used to generate the lithium salt of methyl 3-pyridylmethyl sulphone.

The product was further purified by reverse-phase column chromatography using decreasingly polar mixtures of water and methanol which was acidified with trifluoroacetic acid. The product contained 1.5 equivalents of water and 1 equivalent of trifluoroacetic acid.

Example 18

A solution of p-fluoro-N,N-dimethyl-α-toluenesulphonamide (1.87g) in THF (50ml) was added dropwise to a stirred solution of lithium di-isopropylamide (2M in THF, 4.7ml) in THF (100ml) which had been cooled to -60°C. The mixture was stirred and allowed to warm to -20°C for 15 minutes. The mixture was recooled to -60°C and a solution of pentafluorophenyl o-fluoro-p-{N-[2,7-dimethyl-4-oxo-3-

(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)-amino}benzoate (1.4g) in THF (50ml) was added. The mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The mixture was poured into a saturated aqueous ammonium chloride solution and extracted with ethyl acetate (2x150ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using increasingly polar mixtures of hexane and ethyl acetate as eluent. There was thus obtained N,N-dimethyl-p-fluoro-α-(o-fluoro-p-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)-amino}benzoyl)-α-toluenesulphonamide as a solid (0.55g, 43%).

NMR Spectrum (CD_3SOCD_3) 1.12 (s, 9H), 2.43 (s, 3H), 2.58 (s, 3H), 2.60 (s, 6H), 3.26 (s, 1H), 4.37 (s, 2H), 4.77 (s, 2H), 5.98 (s, 2H), 6.28 (d, 1H), 6.62 (m, 2H), 7.24 (t, 2H), 7.48 (s, 1H), 7.70 (m, 2H), 7.84 (t, 1H).

A mixture of 2N aqueous hydrochloric acid (4ml) and a solution of a portion (0.1g) of the product so obtained in ethyl acetate (8ml) was stirred and heated to reflux for 16 hours. The mixture was cooled to ambient temperature, neutralised by the addition of sodium bicarbonate and extracted with ethyl acetate (2x20ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using increasingly polar mixtures of ethyl acetate and methanol as eluent. The product so obtained was triturated under diethyl ether. There was thus obtained N,N-dimethyl-p-fluoro-α-{o-fluoro-p-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl}-α-toluenesulphonamide (0.064g, 76%), m.p. 198-199°C.

NMR Spectrum (CD_3SOCD_3) 2.34 (s, 3H), 2.44 (s, 3H), 2.63 (s, 6H), 3.27 (s, 1H), 4.37 (s, 2H), 4.77 (s, 2H), 6.31 (d, 1H), 6.66 (m, 2H), 7.25 (t, 2H), 7.44 (s, 1H), 7.69 (m, 3H), 7.86 (t, 1H).

Elemental Analysis: Found C, 60.4; H, 4.9; N, 8.8;
$C_{30}H_{28}F_2N_4O_4S$ $1H_2O$ 0.2EtOAc requires C, 60.2; H, 5.1; N, 9.1%.

Example 19

Using analogous procedures to those described in Example 18, pentafluorophenyl p-{N-[2-methyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}benzoate was reacted with p-fluorobenzyl methyl sulphone to give 4'-fluoro-4-[N-(2-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)-amino]-α-methylsulphonyldesoxybenzoin in 22% yield, m.p. 133-135°C.
NMR Spectrum (CD_3SOCD_3) 2.37 (s, 3H), 2.98 (s, 3H), 3.25 (s, 1H), 4.40 (s, 2H), 4.34 (s, 2H), 6.68 (s, 1H), 6.85 (d, 2H), 7.27 (t, 2H), 7.53 (d, 1H), 7.68 (m, 3H), 7.94 (d, 2H).
Elemental Analysis: Found C, 63.7; H, 5.1; N, 7.0;
$C_{28}H_{24}FN_3O_4S$ 0.3H_2O 0.5EtOAc requires C, 63.5; H, 5.0; N, 7.4%.

Example 20

Using an analogous procedure to that described in Example 16, pentafluorophenyl o-fluoro-p-{N-[2-methyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)-amino}benzoate was reacted with p-fluorobenzyl methyl sulphone to give 2,4'-difluoro-4-[N-(2-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin in 27% yield, m.p. 111-113°C.
NMR Spectrum (CD_3SOCD_3+CD_3CO_2D) 2.37 (s, 3H), 3.0 (s, 3H), 3.11 (s, 1H), 4.41 (s, 2H), 4.88 (s, 2H), 6.20 (s, 1H), 6.66 (m, 2H), 7.24 (t, 2H), 7.62 (m, 4H), 7.86 (t, 1H), 7.98 (d, 1H).
Elemental Analysis: Found C, 60.9; H, 4.5; N, 7.3;
$C_{28}H_{23}F_2N_3O_4S$ 0.8H_2O 0.3EtOAc requires C, 60.8; H, 4.7; N, 7.2%.

The pentafluorophenyl o-fluoro-p-{N-[2-methyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)-amino}benzoate used as a starting material was obtained by the reaction of o-fluoro-p-{N-[2-methyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}benzoic acid (European Patent Application No. 0459730, Example 13 thereof) and pentafluorophenol using an analogous procedure to that mentioned in the portion of Example 4 which is concerned with the preparation of starting materials.

Example 21

Using an analogous procedure to that described in Example 16, pentafluorophenyl o-fluoro-p-{N-[2-methyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)-amino}benzoate was reacted with benzyl methyl sulphone to give 2-fluoro-4-[N-(2-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin in 31% yield, m.p. 106-108°C.

NMR Spectrum (CD_3SOCD_3) 2.38 (s, 3H), 3.0 (s, 3H), 3.11 (s, 1H), 4.37 (s, 2H), 4.85 (s, 2H), 6.16 (s, 1H), 6.52-6.75 (m, 2H), 7.43 (m, 3H), 7.56 (m, 3H), 7.66 (m, 1H), 7.85 (t, 1H), 7.97 (s, 1H).

Elemental Analysis: Found C, 62.0; H, 4.6; N, 8.1;

$C_{28}H_{24}FN_3O_4S$ $1H_2O$ 0.2EtOAc requires C, 62.5; H, 5.2; N, 7.6%.

Example 22

A mixture of 2,4'-difluoro-4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-(4-tert-butoxycarbonylpiperazin-1-ylsulphonyl)desoxybenzoin (0.29g) and trifluoroacetic acid (5ml) was stirred at ambient temperature for 25 minutes. The mixture was evaporated and the residue was triturated under diethyl ether. There was thus obtained 2,4'-difluoro-4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)-amino]-α-(piperazin-1-ylsulphonyl)desoxybenzoin (0.26g), m.p. 151-153°C.

NMR Spectrum (CD_3SOCD_3 + CD_3OD) 2.38 (s, 3H), 2.43 (s, 3H), 2.95-3.09 (m, 2H), 3.28 (m, 2H), 4.36 (s, 2H), 4.77 (s, 2H), 6.28 (s, 1H), 6.58 (m, 2H), 7.20 (t, 2H), 7.46 (s, 1H), 7.62 (m, 3H), 7.82 (s, 1H).

Elemental Analysis: Found C, 49.5; H, 4.2; N, 7.7;

$C_{32}H_{31}F_2N_5O_4S$ $2.3CF_3CO_2H$ requires C, 49.8; H, 3.8; N, 7.9%.

Example 23

n-Butyl lithium (1.6M in hexane, 0.82ml) was added dropwise to a stirred solution of p-fluorobenzyl methyl sulphone (0.23g) in THF (22ml) which had been cooled to -70°C. The mixture was stirred and allowed to warm to -30°C during 1 hour. The mixture was recooled to -70°C and a solution of methyl 5-{N-[2,7-dimethyl-4-oxo-3-

(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)-amino}pyridine-2-carboxylate (0.2g) in THF (12ml) was added. The mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The mixture was poured into a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using increasingly polar mixtures of ethyl acetate and methanol as eluent. There was thus obtained 5-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]pyrid-2-yl p-fluoro-α-methylsulphonylbenzyl ketone (0.14g, 64%), m.p. 154-159°C.

NMR Spectrum (CD_3SOCD_3) 2.32 (s, 3H), 2.45 (s, 3H), 2.99 (s, 3H), 4.47 (s, 2H), 4.85 (s, 2H), 7.1 (s, 1H), 7.2-8.2 (m, 9H), 12.1 (broad s, 1H).

Elemental Analysis: Found C, 63.3; H, 5.2; N, 9.6;
$C_{28}H_{25}FN_4O_4S$ requires C, 63.1; H, 5.1; N, 9.6%.

The methyl 5-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}pyridine-2-carboxylate used as a starting material was obtained as follows:-

A mixture of 6-bromomethyl-2,7-dimethyl-3-(pivaloyloxy-methyl)-3,4-dihydroquinazolin-4-one (1.11g), methyl 5-[N-(prop-2-ynyl)amino]pyridine-2-carboxylate [0.61g; obtained in quantitative yield by treating methyl 5-[N-tert-butoxycarbonyl)-N-(prop-2-ynyl)amino]-pyridine-2-carboxylate (J. Med. Chem., 1991, 1594) with trifluoroacetic acid at 0°C for 1 hour], 2,6-lutidine (0.62g), sodium iodide (0.005g) and DMA (20ml) was stirred and heated to 95°C for 7 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and a 2N aqueous hydrochloric acid solution. The acidity of the aqueous layer was reduced to pH4 by the addition of 2N aqueous sodium hydroxide solution and the solution was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using ethyl acetate as eluent. There was thus obtained methyl 5-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}pyridine-2-carboxylate as a gum

(0.262g).

NMR Spectrum (CD_3SOCD_3) 1.15 (s, 9H), 2.57 (s, 3H), 3.80 (s, 3H), 4.40 (d, 2H), 4.80 (s, 2H), 6.0 (s, 2H), 7.22 (m, 1H), 7.48 (s, 1H), 7.75 (s, 1H), 7.88 (d, 1H), 8.21 (d, 1H).

Example 24

Using an analogous procedure to that described in Example 23, methyl 5-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}pyridine-2-carboxylate was reacted with p-fluoro-N,N-dimethyl-α-toluenesulphonamide to give α-{5-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]pyridine-2-carbonyl}-p-N,N-dimethyl-α-toluenesulphonamide in 33% yield, m.p. 146-151°C.

NMR Spectrum (CD_3SOCD_3) 2.3 (s, 3H), 2.44 (s, 3H), 2.62 (s, 6H), 4.45 (s, 2H), 4.83 (s, 2H), 7.2-8.25 (m, 10H), 12.1 (broad s, 1H).

Elemental Analysis: Found C, 59.8; H, 5.1; N, 11.3;

$C_{29}H_{28}FN_5O_4S$ $1.3H_2O$ requires C, 59.4; H, 5.2; N, 11.9%.

Example 25

Lithium di-isopropylamide (1.5M in cyclohexane, 0.8ml) was added dropwise to a stirred solution of methyl 3-pyridylmethyl sulphone (0.204g) in THF (30ml) which had been cooled to -50°C. The mixture was allowed to warm to -30°C during 30 minutes. The mixture was recooled to -60°C and a solution of pentafluorophenyl 5-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]pyridine-2-carboxylate (0.14g) in DMA (5ml) was added. The mixture was stirred during 4 hours, the temperature being allowed to rise to -20°C. The mixture was poured into a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using increasingly polar mixtures of ethyl acetate and methanol as eluent. The material so obtained was further purified by reverse-phase column chromatography using as eluent decreasingly polar mixtures of water and methanol which had been acidified with a small quantity of acetic acid. There was thus obtained 5-[N-(2,7-dimethyl-4-oxo-3,4-dihydro-

quinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]pyrid-2-yl 1-methylsulphonyl-1-(3-pyridyl)methyl ketone (0.035g, 26%), m.p. 160-164°C.

NMR Spectrum (CD_3SOCD_3) 2.31 (s, 3H), 2.45 (s, 3H), 3.03 (s, 3H), 4.45 (s, 2H), 4.83 (s, 2H), 7.15-8.77 (m, 10H), 12.05 (s, 1H).

Elemental Analysis: Found C, 59.3; H, 5.2; N, 11.6;

$C_{27}H_{25}N_5O_4S$ $1H_2O$ $1CH_3CO_2H$ requires C, 58.5; H, 5.1; N, 11.8%.

The pentafluorophenyl 5-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]pyridine-2-carboxylate used as a starting material was obtained as follows:-

A mixture of methyl 5-{N-[2,7-dimethyl-4-oxo-3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)-amino}pyridine-2-carboxylate (0.26g), 2N aqueous sodium hydroxide solution (20ml) and methanol (10ml) was stirred at ambient temperature for 16 hours. The bulk of the methanol was evaporated and the residual aqueous solution was acidified to pH4 by the addition of 2N aqueous hydrochloric acid. The resultant precipitate was isolated, washed in turn with water and diethyl ether and dried. There was thus obtained 5-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]pyridine-2-carboxylic acid (0.143g).

After appropriate repetition of the preceding reaction, the carboxylic acid (0.75g) so obtained was dissolved in DMA (10ml). The solution was cooled to 10°C and pyridine (0.49ml) and pentafluorophenyl trifluoroacetate (1.06ml; prepared by the reaction of pentafluorophenol and trifluoroacetic acid) were added in turn. The mixture was stirred for 2 hours and allowed to warm to ambient temperature. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using ethyl acetate as eluent. There was thus obtained pentafluorophenyl 5-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]pyridine-2-carboxylate (0.82g).

NMR Spectrum (CD_3SOCD_3) 2.33 (s, 3H), 2.46 (s, 3H), 4.50 (d, 2H), 4.87 (s, 2H), 7.25-8.35 (m, 5H), 12.10 (broad s, 1H).

Example 26

The procedure described in Example 25 was repeated except that p-fluorobenzyl 4-pyridyl sulphone was used in place of methyl 3-pyridylmethyl sulphone. There was thus obtained 5-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]pyrid-2-yl p-fluoro-α-(4-pyridylsulphonyl)benzyl ketone in 31% yield, m.p. 158-162°C.

NMR Spectrum ($CDCl_3$) 2.32 (m, 1H), 2.48 (2 s's, 6H), 4.22 (d, 2H), 4.69 (s, 2H), 6.95-8.75 (m, 14H).

Elemental Analysis: Found C, 62.7; H, 4.9; N, 10.1;

$C_{32}H_{26}FN_5O_4S$ 1.2H_2O requires C, 62.3; H, 4.6; N, 11.3%.

Example 27

The procedure described in Example 25 was repeated except that N,N-dimethyl-3-pyridylmethanesulphonamide was used in place of methyl 3-pyridylmethyl sulphone. There was thus obtained 5-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)-amino]pyrid-2-yl 1-(N,N-dimethylsulphamoyl)-1-(3-pyridyl)methyl ketone in 81% yield, m.p. 155-160°C.

NMR Spectrum (CD_3SOCD_3) 2.22 (s, 3H), 2.35 (s, 3H), 2.54 (s, 6H), 4.39 (d, 2H), 4.76 (s, 2H), 7.2-8.7 (m, 10H), 12.0 (broad s, 1H).

Elemental Analysis: Found C, 60.6; H, 5.2; N, 14.9;

$C_{28}H_{28}N_6O_4S$ 0.5H_2O requires C, 60.7; H, 5.3; N, 15.2%.

The N,N-dimethyl-3-pyridylmethanesulphonamide used as a starting material was obtained as follows:-

A mixture of 3-(chloromethyl)pyridine hydrochloride (15g), potassium thioacetate (24g) and acetone (220ml) was stirred at ambient temperature for 22 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography to give 3-(acetylthiomethyl)pyridine (14.1g, 92%).

A portion (6.6g) of the material so obtained and sodium acetate (12g) were dissolved in a mixture of glacial acetic acid (140ml) and water (30ml). The mixture was cooled to 10°C. Chlorine gas (14g) was passed into the solution. The mixture was evaporated and the residue was triturated under ethyl acetate. There was thus obtained 3-pyridylmethanesulphonyl chloride which was used without

further purification.
NMR Spectrum (CD_3SOCD_3) 4.0 (s, 2H), 8.04 (m, 1H), 8.55 (d, 1H), 8.80 (m, 2H).

The material so obtained was dissolved in THF (200ml) and the solution was stirred and cooled in an ice-bath while dimethylamine gas was led into the solution. When the exothermic reaction ceased, the mixture was stirred at ambient temperature for 1.5 hours. Ethyl acetate was added and the mixture was filtered. The filtrate was evaporated and the residue was purified by column chromatography to give N,N-dimethyl-3-pyridylmethanesulphonamide (1.96g), m.p. 96-97°C.
NMR Spectrum (CD_3SOCD_3) 2.75 (s, 6H), 4.50 (s, 2H), 7.42 (m, 1H), 7.83 (m, 1H), 8.58 (m, 2H).

Example 28

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically-acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:-

(a)

Tablet I	mg/tablet
Compound X..................................	100
Lactose Ph.Eur..............................	182.75
Croscarmellose sodium.......................	12.0
Maize starch paste (5% w/v paste)............	2.25
Magnesium stearate..........................	3.0

(b)

Tablet II	mg/tablet
Compound X..................................	50
Lactose Ph.Eur..............................	223.75
Croscarmellose sodium.......................	6.0
Maize starch................................	15.0
Polyvinylpyrrolidone (5% w/v paste)..........	2.25
Magnesium stearate..........................	3.0

(c) Tablet III

	mg/tablet
Compound X..................................	1.0
Lactose Ph.Eur..............................	93.25
Croscarmellose sodium.......................	4.0
Maize starch paste (5% w/v paste)...........	0.75
Magnesium stearate..........................	1.0

(d) Capsule

	mg/capsule
Compound X..............................	10 mg
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

(e) Injection I

	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid (to adjust pH to 7.6)	
Polyethylene glycol 400..................	4.5% w/v
Water for injection to 100%	

(f) Injection II

	(10 mg/ml)
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection to 100%	

(g) Injection III

	(1mg/ml, buffered to pH6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection to 100%	

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a) to (c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

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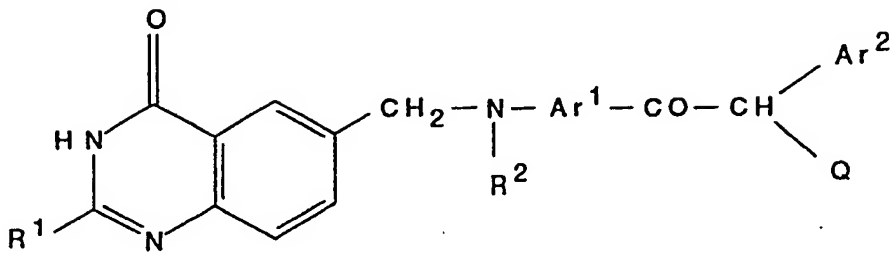
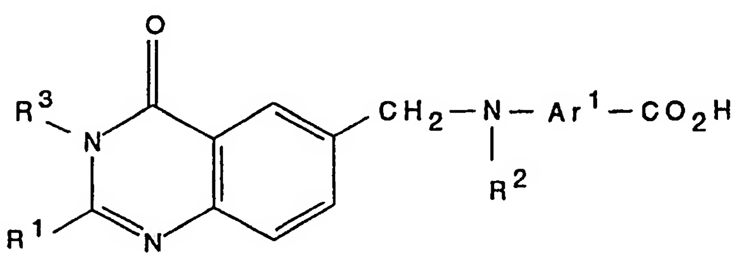
CHEMICAL FORMULAE



I



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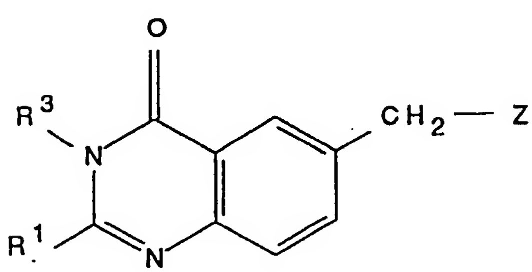
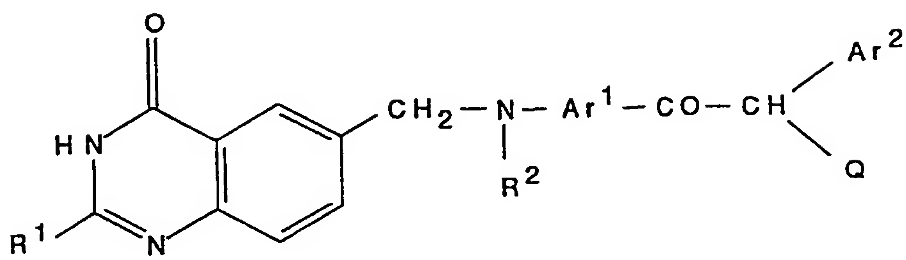


III

CLAIMS

1. A quinazoline derivative of the formula I



I

wherein R^1 is hydrogen, amino, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, piperidino, morpholino, piperazin-1-yl, 4-[(1-4C)alkyl]piperazin-1-yl, 4-[(2-4C)alkanoyl]piperazin-1-yl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, piperidino-(1-4C)alkyl, morpholino-(1-4C)alkyl, piperazin-1-yl-(1-4C)alkyl, 4-[(1-4C)alkyl]piperazin-1-yl-(1-4C)alkyl, 4-[(2-4C)alkanoyl]piperazin-1-yl-(1-4C)alkyl, N-[hydroxy-(2-4C)alkyl]amino-(1-4C)alkyl, N-[hydroxy-(2-4C)alkyl]-N-(1-4C)alkylamino-(1-4C)alkyl, N,N-di-[hydroxy-(2-4C)alkyl]amino-(1-4C)alkyl, N-[(1-4C)alkoxy-(2-4C)alkyl]amino-(1-4C)alkyl, N-[(1-4C)alkoxy-(2-4C)alkyl]-N-(1-4C)alkylamino-(1-4C)alkyl, N,N-di-[(1-4C)alkoxy-(2-4C)alkyl]amino-(1-4C)alkyl, N-[(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl, N-[(1-4C)alkylamino-(2-4C)alkyl]-N-(1-4C)alkylamino-(1-4C)alkyl, N,N-di-[(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl, N-[di-(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl, N-[di-(1-4C)alkylamino-(2-4C)alkyl]-N-(1-4C)alkylamino-(1-4C)alkyl, N,N-di-[di-(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)alkyl, carboxy-(2-4C)alkanoyloxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(2-4C)alkanoyloxy-(1-4C)alkyl, hydroxy-(2-4C)alkoxy-(1-4C)alkyl or (1-4C)alkoxy-(2-4C)alkoxy-(1-4C)alkyl;

the quinazoline ring may optionally bear at the 5-, 7- or 8-position one further substituent selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy;
R^2 is hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-4C)alkynyl, hydroxy-(2-4C)alkyl, halogeno-(2-4C)alkyl or cyano-(1-4C)alkyl;
Ar^1 is phenylene or a 5- or 6-membered aromatic heterocyclene ring which contains up to 3 heteroatoms selected from nitrogen and sulphur, each of which may optionally bear one or two substituents selected from halogeno, hydroxy, amino, nitro, cyano, trifluoromethyl, (1-4C)alkyl and (1-4C)alkoxy;
Ar^2 is phenyl or heteroaryl which may optionally bear one or two substituents selected from halogeno, hydroxy, amino, nitro, cyano, trifluoromethyl, (1-4C)alkyl and (1-4C)alkoxy; and
Q is nitro, cyano, carbamoyl, sulphamoyl, (1-4C)alkoxycarbonyl, di-[(1-4C)alkoxy]phosphoryl, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, phenyl-(1-4C)alkylthio, phenyl-(1-4C)alkylsulphinyl, phenyl-(1-4C)-alkylsulphonyl, heteroarylthio, heteroarylsulphinyl, heteroarylsulphonyl, heteroaryl-(1-4C)alkylthio, heteroaryl-(1-4C)alkylsulphinyl, heteroaryl-(1-4C)alkylsulphonyl, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, N-(1-4C)alkylsulphamoyl, N,N-di-[(1-4C)alkyl]sulphamoyl, morpholino-sulphonyl, piperidinosulphonyl, piperazin-1-ylsulphonyl or 4-(1-4C)-alkylpiperazin-1-ylsulphonyl, and when Q is a group comprising a phenyl or heteroaryl group, said phenyl or heteroaryl group may optionally bear one substituent selected from halogeno, cyano, hydroxy, amino, (1-4C)alkyl and (1-4C)alkoxy;
and wherein the heteroaryl group when Ar^2 is heteroaryl, or the heteroaryl group when Q is a heteroaryl-containing group, is a 5- or 6-membered heteroaryl ring which contains 1 or 2 nitrogen heteroatoms and optionally contains a further heteroatom selected from nitrogen, oxygen and sulphur;
or a pharmaceutically-acceptable salt thereof.

2. A quinazoline derivative of the formula I as defined in claim 1 wherein, in addition, Q is 4-(1-4C)alkoxycarbonylpiperazin-1-

ylsulphonyl, N-[amino-(2-4C)alkyl]sulphamoyl, N-[(1-4C)alkylamino-(2-4C)alkyl]sulphamoyl, N-{di-[(1-4C)alkyl]amino-(2-4C)alkyl}sulphamoyl, N-(1-4C)alkyl-N-[amino-(2-4C)alkyl]sulphamoyl, N-(1-4C)alkyl-N-[(1-4C)alkylamino-(2-4C)alkyl]sulphamoyl or N-(1-4C)alkyl-N-{di-[(1-4C)alkyl]amino-(2-4C)alkyl}sulphamoyl;
or a pharmaceutically-acceptable salt thereof.

3. A quinazoline derivative of the formula I as claimed in claim 1 wherein R^1 is methyl, hydroxymethyl, methoxymethyl, methylaminomethyl, dimethylaminomethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl or 4-methylpiperazin-1-ylmethyl;
the quinazoline ring may optionally bear a 7-fluoro, 7-chloro or 7-methyl substituent;
R^2 is methyl, ethyl, propyl, prop-2-enyl or prop-2-ynyl;
Ar^1 is 1,4-phenylene which may optionally bear one fluoro substituent, or Ar^1 is thiophene-2,5-diyl or thiazole-2,5-diyl with the group -CO-CH(Ar^2)(Q) in the 2-position;
Ar^2 is phenyl which may optionally bear a substituent selected from fluoro, chloro, nitro, trifluoromethyl or methyl; and
Q is nitro, cyano, carbamoyl, sulphamoyl, methoxycarbonyl, ethoxycarbonyl, dimethoxyphosphoryl, diethoxyphosphoryl, methylsulphinyl, isopropylsulphinyl, methylsulphonyl, isopropylsulphonyl, phenylsulphinyl, phenylsulphonyl, benzylsulphinyl, benzylsulphonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, N-methylsulphamoyl, N,N-dimethylsulphamoyl or morpholinosulphonyl;
or a pharmaceutically-acceptable salt thereof.

4. A quinazoline derivative of the formula I as claimed in claim 1 or claim 2
wherein R^1 is methyl;
the quinazoline ring may optionally bear a 7-methyl substituent;
R^2 is methyl or prop-2-ynyl;
Ar^1 is 1,4-phenylene, 2-fluoro-1,4-phenylene (with the group -CO-CH(Ar^2)(Q) in the 1-position) or pyridine-2,5-diyl (with the group -CO-CH(Ar^2)(Q) in the 2-position);
Ar^2 is phenyl, 3-fluorophenyl, 4-fluorophenyl, 3-nitrophenyl,

4-cyanophenyl, 2-pyridyl or 3-pyridyl; and
Q is diethoxyphosphoryl, isopropylsulphinyl, methylsulphonyl, isopropylsulphonyl, phenylsulphonyl, benzylsulphonyl, 4-pyridylsulphonyl, N-methylsulphamoyl, N,N-dimethylsulphamoyl, morpholinosulphonyl, piperazin-1-ylsulphonyl or N-methyl-N-(2-dimethylaminoethyl)sulphamoyl;
or a pharmaceutically-acceptable salt thereof.

5. A quinazoline derivative of the formula I as claimed in claim 1 or claim 2
wherein R^1 is methyl;
the quinazoline ring may optionally bear a 7-methyl substituent;
R^2 is methyl or prop-2-ynyl;
Ar^1 is 1,4-phenylene, 2-fluoro-1,4-phenylene (with the group -CO-CH(Ar^2)(Q) in the 1-position) or pyridine-2,5-diyl (with the group -CO-CH(Ar^2)(Q) in the 2-position);
Ar^2 is phenyl, 3-fluorophenyl, 4-fluorophenyl or 3-pyridyl; and
Q is diethoxyphosphoryl, isopropylsulphinyl, methylsulphonyl, isopropylsulphonyl, phenylsulphonyl, benzylsulphonyl, 4-pyridylsulphonyl, N-methylsulphamoyl, N,N-dimethylsulphamoyl or morpholinosulphonyl;
or a pharmaceutically-acceptable salt thereof.

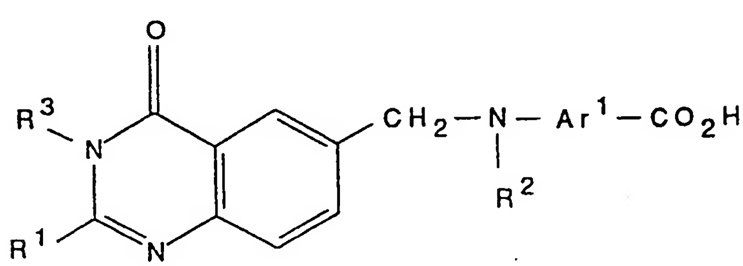
6. A quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in claim 1, selected from:-
4-[N-(2-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin,
4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin and
N,N-dimethyl-α-{p-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl}-α-toluenesulphonamide.

7. A quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in claim 1 or claim 2, selected from:-

4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-isopropylsulphonyldesoxybenzoin, N,N-dimethyl-p-fluoro-α-{p-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl}-α-toluenesulphonamide, 2,4'-difluoro-4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin, N,N-dimethyl-p-fluoro-α-{o-fluoro-p-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl}-α-toluenesulphonamide, 4'-fluoro-4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin, 2,4'-difluoro-4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-morpholinosulphonyldesoxybenzoin, α-{5-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]pyridine-2-carbonyl}-p-fluoro-N,N-dimethyl-α-toluenesulphonamide and 4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]phenyl 1-methylsulphonyl-1-(3-pyridyl)methyl ketone.

8. A process for the preparation of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 7 which comprises:-

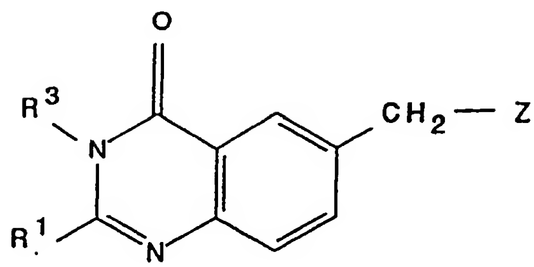
(a) the reaction of an acid of the formula II



II

or a reactive derivative thereof, wherein R^3 is hydrogen or a protecting group, with a compound of the formula Ar^2-CH_2-Q;

(b) the reaction of a compound of the formula III



III.

wherein R^3 has the meaning defined above and Z is a displaceable group, with an amine of the formula:

$$HNR^2\text{-}Ar^1\text{-}CO\text{-}CH(Ar^2)(Q)$$

(c) for the production of a compound of the formula I wherein Q is a group which comprises a sulphinyl or sulphonyl group, the oxidation of the corresponding compound of the formula I wherein Q is a group which comprises a thio group;

(d) for the production of a compound of the formula I wherein R^1 is amino-(1-4C)alkyl or substituted-amino-(1-4C)alkyl, the reaction of a compound of the formula I wherein R^1 is hydroxy-(1-4C)alkyl, or a reactive derivative thereof, with ammonia or a substituted-amine;

(e) for the production of a compound of the formula I wherein R^1 is (2-4C)alkanoyloxy-(1-4C)alkyl or substituted-(2-4C)alkanoyloxy-(1-4C)alkyl, the reaction of a compound of the formula I wherein R^1 is hydroxy-(1-4C)alkyl with an acylating reagent; and

(f) for the production of a compound of the formula I wherein Q is a piperazin-1-ylsulphonyl group, the cleavage of a compound of the formula I wherein Q is a 4-(1-4C)alkoxycarbonylpiperazin-1-yl group;

and when a pharmaceutically-acceptable salt of a compound of the formula I is required, it may be obtained by reaction of said compound with a suitable acid or base using a conventional procedure; and when an optically active form of a compound of the formula I is required, it may be obtained by carring out one of the aforesaid processes using an optically active starting material, or by resolution of a racemic form of said compound using a conventional procedure.

9. A pharmaceutical composition which comprises a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 7 in association with a pharmaceutically-acceptable diluent or carrier.

10. The use of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 7 in the manufacture of a novel medicament for use in the production of an anti-tumour effect in a warm-blooded animal.

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tents Act 1977
Examiner's report to the Comptroller under Section 17
(The Search report)

- 69 -

Application number
GB 9320077.2

Relevant Technical Fields

(i) UK Cl (Ed.M) C2C CRM CSJ CLW CLZ

(ii) Int Cl (Ed.5) C07D

Databases (see below)
(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) Online database: CAS online

Search Examiner
D S LUCAS

Date of completion of Search
16 DECEMBER 1993

Documents considered relevant following a search in respect of Claims :-
1-10

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
A	EP 0365763 A (AGOURO) see Claim 1	1-10
A	EP 0316657 A (WARNER LAMBERT) see Claim 1	1-10

Databases:The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).